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(54) Title: NUCLEIC ACIDS ENCODING ZINC METALLOPROTEASES

ADAM-TS RELATED PROTEIN-1 (ADAM-TSR1) ADAM-TS1 951 e.a. ADAM-TSR1 525 a.e. N- 1

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SIGNAL PEPTIDE

PRO-DOMAIN

METALLOPROTEASE DOMAIN

DISINTEGRIN-LIKE DOMAIN

THROMBOSPONDIN TYPE I REPEAT

CYSTEINE-RICH DOMAIN
CYSTEINE-POOR DOMAIN

UNIQUE DOMAINS

(57) Abstract: Isolated mammalian proteins having disintegrin-like and metalloprotease domains with thrombospondin type I motifs, i.e., ADAMTS proteins, are provided. The proteins are ADAMTS-5, ADAMTS-6, ADAMTS-7, ADAMTS-8, ADAMTS-9 and ADAMTS-10, collectively referred to as "ADAMTS-N". The present invention also provides isolated polynucleotides which encode an ADAMTS-N protein or a variant thereof, polynucleotide sequences complementary to such polynucleotides, vectors containing such polynucleotides, and host cells transformed or transfected with such vectors. The present invention also relates to antibodies which are immunospecific for one or more of the ADAMTS-N proteins. The present invention also relates to a protein referred to hereinafter as ADAMTS-R1 (ADAM-TS Related protein-1) and the polynucleotides which encode such protein.

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NUCLEIC ACIDS ENCODING ZINC METALLOPROTEASES

Background of the Invention

This invention relates to isolated nucleic acid -molecules

5 which encode proteins belonging to a zinc metalloprotease family.

The zinc metalloproteases have been implicated in a variety of diseases and development disorders that involve* enhanced or depressed proteolysis of components of the extracellular matrix, receptors, or other extracellular molecules.

- More particularly, the invention relates to isolated nucleic acid molecules encoding proteins belonging to a subfamily of zinc metalloproteases referred to as "ADAMTS", an abbreviation for A Disintegrin-like And Metalloprotease domain with ThromboSpondin type I motifs. Proteins in the ADAMTS subfamily all possess a Zn 15 protease catalytic site consensus sequence (HEXXH+H), which suggests
- an intact catalytic activity for each of these proteins. The ADAMTS proteins also have putative N-terminal signal peptides and lack transmembrane domains, which suggests that the proteins in this subfamily are secreted. The proteins in the ADAMTS subfamily also
- 20 possess at least one thrombospondin type (TSP1) motif, which suggests a binding of these proteins to components of the extracellular matrix (ECM) or to cell surface components.

Members of the ADAMTS subfamily of proteins are ADAMTS-1,
ADAMTS-2, ADAMTS-3, and ADAMTS-4. ADAMTS-1 protein is selectively
25 expressed in colon 26 adenocarcinoma cachexigenic sublines. ADAMTS-1
mRNA is induced by the inflammatory cytokine interleukin-1 in vitro
and by intravenous administration of lipopolysaccharide in vivo.
Thus, the ADAMTS-1 protein is believed to play a role in tumor
cachexia and inflammation.

The ADAMTS-2 protein is also known as procollagen I/H aminopropetide processing enzyme or PCINP. The ADAMTS-2 protein catalyzes

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cleavage of native triple-helical procollagen I and procollagen II.

The ADAMTS-2 protein also has an affinity for collagen XIV. Lack of the ADAMTS-2 protein is known to cause dermatosparaxis in cattle, or Ehlers-Danlos syndrome type VIIC (EDS-VIIC) in humans. EDS-VIIC is characterized clinically by severe skin fragility, and biochemically by the presence in skin of procollagen which is incompletely processed at the amino terminus. Thus, it is believed that the ADAMTS-2 protein plays a role in processing of procollagen to mature collagen, an essential step for correct assembly of collagen into 10 collagen fibrils. The ADAMTS-3 protein is similar in sequence to ADAMTS-2 and may have similar function.

The ADAMTS-4 protein catalyzes cleavage of the core protein of the extracellular matrix proteoglycan, aggrecan. Aggrecan degradation is an important factor in the erosion of articular cartilage in arthritic disease. Aggrecan fragments have been identified in cultures undergoing cartilage matrix degradation and in arthritic synovial fluids. Therefore, overexpression or activation 10 of ADAMTS-4 protein may be related to both inflammatory and non-inflammatory arthritis.

- On the basis of the structure, location, and the demonstrated proteolytic activity of ADAMTS proteins 1-4, it is expected that other members of the ADAMTS subfamily play a role in the cleavage of proteoglycan core proteins that are found in the extracellular matrix, such as, for example, versican, brevican, neuracan, NG-2,
- 25 aggrecan, as well as molecules such as collagen. It is also expected that other members of the ADAMTS subfamily play a role in embryogenesis, implantation of a fertilized egg, angiogenesis, arthritic degradation of cartilage, inflammation, nerve regeneration, tumor growth, and metastases.
- Thus, it is desirable to have other members of the ADAMTS

subfamily of proteins, the nucleic acids that encode such proteins, and antibodies that are specific for such proteins. Such molecules are useful research tools for studying development of the extracellular matrix during embryogenesis and fetal development, and 5 for studying disorders or diseases that are characterized by improper development of the extracellular matrix or enhanced or reduced destruction of the extracellular matrix. Such molecules, particularly the nucleic acids and the antibodies, are also useful tools for diagnosing such diseases or for monitoring the efficacy of therapeutic agents that have been developed to treat such diseases.

Summary of the Invention

The present invention provides novel, isolated, and substantially purified proteins having the characteristics of an 15 ADAMTS protein. The novel proteins are referred to hereinafter individually as "ADAMTS-5", "ADAMTS-6", "ADAMTS-7", "ADAMTS-8", "ADAMTS-9" and "ADAMTS-10", and collectively as "ADAMTS-N". In one embodiment, the ADAMTS-5 protein is a mature mouse protein which comprises amino acid 231 through amino acid 930 of the sequence set 20 forth set forth in SEQ ID NO: 2. In another embodiment, ADAMTS-5 is a human ADAMTS-5 protein which comprises amino acid 1 through amino acid 518 of the sequence set forth in SEQ ID NO: 4. In one embodiment, mature human ADAMTS-6 protein comprises amino acid 245 through amino acid 860 of SEQ ID NO: 6. In one embodiment, mature 25 human ADAMTS-7 protein comprises amino acid 233 through amino acid 997 of the sequence set forth in SEQ ID NO: 8. In one embodiment, mature ADAMTS-8 protein is a mouse protein which comprises amino acid 229 through amino acid 905 of the sequence set forth in SEQ ID NO: In another embodiment, ADAMTS-8 protein is a human protein which 30 comprises amino acid 1 through amino acid 245 of the sequence set forth in SEQ ID NO: 12. In one embodiment, mature ADAMTS-9 protein

is a human protein which comprises amino acid 236 through amino acid 1882 of the sequence set forth in SEQ ID NO: 14. In another embodiment, ADAMTS-9 protein is a mouse protein which comprises amino acid 1 through amino acid 974 of the sequence set forth in SEQ ID NO:

- 5 16. In one embodiment, mature ADAMTS 10 protein is a human protein which comprises amino acid 212 through amino acid 1081 of the sequence set forth in SEQ ID NO: 18. In another embodiment, ADAMTS-10 protein is a mouse protein which comprises amino acid 1 through amino acid 547 of the sequence set forth in SEQ ID NO: 20.
- The present invention also provides isolated polynucleotides which encode an ADAMTS-N protein or a variant thereof, polynucleotide sequences complementary to such polynucleotides, vectors containing such polynucleotides, and host cells transformed or transfected with such vectors. The present invention also relates to antibodies which are immunospecific for one or more of the ADAMTS-N proteins. The present invention also relates to a protein referred to hereinafter as ADAMTS-R1 (ADAM-T-S Related protein-1) and the polynucleotides which encode such protein. In one embodiment, the ADAMTS-R1 protein comprises amino acid 1 through amino acid 525 of the sequence set

Brief Description of the Drawings
Figure 1 shows an amino acid sequence (SEQ ID NO:2) of a full-length
mouse ADAMTS-5 protein and a nucleic acid sequence (SEQ ID NO: 1)
which encodes such protein.

25 Figure 2 shows an amino acid sequence (SEQ ID NO:4) of a partial human ADAMTS-5 protein and a nucleic acid sequence (SEQ ID NO: 3) which encodes such protein.

Figure 3 shows an amino acid sequence (SEQ ID NO:6) of a full-length human ADAMTS-6 protein and a nucleic acid sequence (SEQ ID NO:5)

30 which encodes such protein.

Figure 4 shows an amino acid sequence (SEQ ID NO:8) of a full-length human ADAMTS-7 protein and a nucleic acid sequence (SEQ ID NO:7) which encodes such protein.

Figure 5 shows an amino acid sequence (SEQ ID NO: 10) of a full-

5 length mouse ADAMTS-8 protein and a nucleic acid sequence (SEQ ID NO:9) which encodes such protein.

Figure 6 shows an amino acid sequence (SEQ ID NO: 12) of a partial human ADAMTS-8 protein and a nucleic acid sequence (SEQ ID NO: 11) which encodes such amino acid sequence.

10 Figure 7 shows an amino acid sequence (SEQ ID NO: 14), of a full-length human ADAMTS-9 protein and a nucleic acid sequence (SEQ ID NO: 13) Which encodes such protein.

Figure 8 shows an amino acid sequence (SEQ ID NO: 16) of a partial mouse ADAMTS-9 protein and a nucleic acid sequence (SEQ ID NO: 15)

15 which encodes such amino acid sequence.

Figure 9 shows an amino acid sequence (SEQ ID NO:18) of a full-length human ADAMTS-10 protein and a nucleic acid sequence (SEQ ID NO: 17) which encodes such protein.

Figure 10 show's an amino acid sequence (SEQ ID NO:20) of a partial

- 20 mouse ADAMTS-10 protein and a nucleic acid sequence (SEQ ID NO,: 19) which encodes such amino acid sequence.
 - Figure 11 shows an amino acid sequence (SEQ ID NO:22) of a full length ADAMTS-R1 protein and a nucleic acid sequence (SEQ ID NO: 21) which encodes such protein.
- 25 Figure 12 depicts the cloning strategy used for isolation of a. mouse and human ADAMTS-5 cDNAs b. human ADAMTS-6 cDNA and c. human ADAMTS-7 cDNA. The domain organization of each protein relative to the cDNA clones (thin line) is shown as is the extent of overlap between clones. The original I.M.A.G.E. clones are underlined. Intronic 30 regions of incompletely spliced transcripts are shown by the angled

dotted lines. DNA scale marker (in bp) and amino acid scale marker are at upper right. Location of the probe used for in situ hybridization (ISH) is shown in a.

Figure 13 shows the predicted amino acid sequences of a. the mouse 5 and human ADAMTS-5 proteins (alignment shows mouse sequence above, partial human sequence below) b. ADAMTS-6, and c. ADAMTS-7. The active-site sequences and proposed Met-turn are enclosed in boxes. Potential furin cleavage site(s) are indicated by arrows.

Thrombospondin type-1 modules are underlined. Potential sites for N-

- 10 inked glycosylation are overlined. Cysteine residues within the context of an MMP-like "cysteine switch" are indicated by the solid circles. Other cysteine residues are indicated by asterisks. The prodomain extends until the furin cleavage site, and the catalytic domain extends from the furin cleavage site to the approximate start
- 15 of the disintegrin-like sequence (Dis). The start of the spacer domain is indicated; the region between the N-terminal TS domain and the spacer domain is the cysteine-rich domain. The single letter amino acid code is used.

Figure 14 shows Northern analysis of expression of ADAMTS-5, 6 and 7.

- 20 RNA kilobase markers are shown at left of each autoradiogram, and tissue origin is indicated above each lane. a. Mouse embryo northern blots. b. Human multiple adult tissue northern blots.
 - Figure 15 is a schematic representation of the domain structure of ADAMTS-R1 protein as compared to ADAMTS-1 protein.
- 25 Figure 16 shows an amino acid sequence (SEQ ID NO: 24) of an alternative embodiment of a full-length human ADAMTS-10 protein and a nucleic acid sequence (SEQ ID NO: 23) which encodes such protein.

 Figure 17 shows an amino acid sequence (SEQ ID NO: 26) of an alternative embodiment of human ADAMTS-9, which is a full-length

 30 protein designated as human ADAMTS-9b and a nucleic acid sequence

" (SEQ ID NO: 25) which encodes such protein.

Figure 18 is a schematic representation of the domain structure of human ADAMTS-9b protein as compared to human and mouse ADAMTS-9 protein.

5 <u>Detailed Description of the Invention</u> ADAMTS-N Proteins

The present invention relates to novel, isolated, substantially purified, mammalian proteins belonging to the ADAMTS subfamily of metalloproteases. As used herein, the term "substantially purified"

10 refers to a protein that is removed from its natural environment, isolated or separated, and at least 60% free, preferably 75% free, and most preferably 90% free from other components with which it is naturally associated.

The novel mammalian proteins are ADAMTS-5, ADAMTS-6, ADAMTS-7, 15 ADAMTS-8, ADAMTS-9 and ADAMTS-10, collectively ADAMTS-N. In one embodiment, the ADAMTS-5 protein is a mature mouse protein which comprises amino acid 231 through amino acid 930 of the sequence set forth in SEQ ID NO: 2. In another embodiment, the ADAMTS-5 protein is a human protein which comprises amino acid 1 through amino acid 20 518 of the sequence set forth in SEQ ID NO: 4. In one embodiment, .. ADAMTS-6 protein is a mat-Lire human protein which comprises amino acid 245 through amino acid 860 of SEQ ID NO:6. In one embodiment, the ADAMTS-7 protein is a mature human protein which comprises amino acid 233 through amino acid 997 of the sequence set forth in SEQ ID 25 NO: 8. In one embodiment, the ADAMTS-8 protein is a mature mouse protein which comprises amino acid 229 through amino acid 905 of the sequence set forth in SEQ ID NO: 10. In another embodiment, the ADAMTS-8 protein is a human protein which comprises amino acid 1 through amino acid 245 of the sequence set forth in SEO ID NO: 12. 30 In one embodiment, the ADAMTS-9 is a mature human protein which

comprises amino acid 236 through amino acid 1882 of the sequence set

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forth in SEQ ID NO: 14. In another embodiment, the ADAMTS-9 protein is a mouse protein which comprises amino acid 1 through amino acid 874 of the sequence set forth in SEQ ID NO: 16. In another embodiment, the ADAMTS-9 designated ADAMTS-9b is a human protein 5 which is comprised of 1934 amino acids as set forth in SEQ ID NO 26. In one embodiment, the ADAMTS-10 protein is a mature human protein which comprises amino acid 212 through amino acid 1081 of the sequence set forth in SEQ ID NO: 18. In another embodiment the ADAMTS- 10 protein is a mouse protein which comprises amino acid 1 . 10 through amino acid 525 of the sequence set forth in SEQ ID NO:20. In another embodiment, the ADAMTS-10 protein is a human protein which is comprised of 1072 amino acids as set forth in SEQ ID NO 24.

terminus comprise a signal sequence followed by a putative pro region

15 which contains a consensus sequence for furin cleavage (except for

ADAMTS-10), a catalytic domain, a domain of 60-90 residues with 35 to

45% similarity to snake venom disintegrins, a TS module, a cysteine

rich domain containing multiple conserved cysteine residues, a spacer

domain, and one or multiple C terminal TS modules. (See Figure 12.)

20 As determined using the BLAST software from the National Center for

Biotechnology Information, the predicted mature forms of the ADAMTS-N

proteins show an overall 20-30% similarity to each other and to

ADAMTS-1-4, although this may be considerably higher or lower for

individual domains as described below.

25 The ADAMTS-N proteins also encompass variants of the ADAMTS-N proteins shown in Figs. 1-10. A "variant" as used herein, refers to a protein whose amino acid sequence is similar to one of the amino acid sequences shown in Figs. 1-10, hereinafter referred to as the reference amino acid sequence, but does not have 100% identity with 30 the reference sequence. The variant protein has an altered sequence

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in which one or more of the amino acids in the reference sequence is deleted or substituted, or one or more amino acids are inserted into the sequence of the reference amino acid sequence. As a result of the alterations, the variant protein has an amino acid sequence which 5 is at least 95% identical to the reference sequence, preferably, at least 97% identical, more preferably at least 98% identical, most preferably at least 99% identical to the reference sequence. Variant sequences which are at least 95% identical have no more than 5 alterations, i.e. any combination of deletions, insertions or 10 substitutions, per 100 amino acids of the reference sequence. Percent identity is determined by comparing the amino acid sequence of the variant with the reference sequence using MEGALIGN project in the DNA STAR program. Sequences are aligned for identity calculations using the method of the software basic local alignment 15 search tool in the BLAST network service (the National Center for Biotechnology Information, Bethesda, MD) which employs the method of Altschul, S. F., Gish, W., Miller, W., Myers, E. W. & Lipman, D. J. (1990) J. Mol. Biol. 215, 403-410. Identities are calculated by the Align program (DNAstar, Inc.) In all cases, internal gaps and amino 20 acid insertions in the candidate sequence as aligned are not ignored when making the identity calculation.

while it is possible to have nonconservative amino acid substitutions, it is preferred that the substitutions be conservative amino acid substitutions, in which the substituted amino acid has 25 similar structural or chemical properties with the corresponding amino acid in the reference sequence. By way of example, conservative amino acid substitutions involve substitution of one aliphatic or hydrophobic amino acids, e.g. alanine, valine, leucine and isoleucine, with another; substitution of one hydroxyl-containing 30 amino acid, e.g. serine and threonine, with another; substitution of

one acidic residue, e.g. glutamic acid or aspartic acid, with another; replacement of one amide-containing residue, e.g. asparagine and glutamine, with another; replacement of one aromatic, residue, e.g. phenylalanine and tyrosine, with another; replacement of one basic residue, e.g. lysine, arginine and histidine, with another; and replacement of one small amino acid, e.g., alanine, serine, threonine, methionine, and glycine, with another.

The alterations are designed not to abolish the immunoreactivity of the variant protein with antibodies that bind to the reference protein. Guidance in determining which amino acid residues may be substituted, inserted or deleted without abolishing immunoreactivity of the variant protein with an antibody specific for the respective reference protein are found using computer programs well known in the art, for example, DNASTAR software.

The ADAMTS-N proteins also encompass fusion proteins comprising an ADAMTS-N protein and a tag, i.e., a second protein or one or more amino acids, preferably from about 2 to 65 amino acids, more preferably from about 34 to about 62 amino acids, which are added to the amino terminus of, the carboxy terminus of, or any point within 20 the amino acid sequence of an ADAMTS-N protein, or a variant of such protein. Typically, such additions are made to stabilize the resulting fusion protein or to simplify purification of an expressed recombinant form of the corresponding ADAMTS-N protein or variant of such protein. Such tags are known in the art. Representative 25 examples of such tags include sequences which encode a series of histidine residues, the epitope tag FLAG, the Herpes simplex glycoprotein D, beta-galactosidase, maltose binding protein, or glutathione S-transferase.

The ADAMTS-N proteins also encompass ADAMTS-N proteins in which 30 one or more amino acids, preferably no more than 10 amino acids, in

the respective ADAMTS-N protein are altered by posttranslation processes or synthetic methods. Examples of such modifications include, but are not limited to, acetylation, amidation, ADP-ribosylation, covalent attachment of flavin, covalent attachment of a flavin, covalent attachment of a flavin, covalent attachment of a nucleotide or a lipid, cross-linking gamma-carboxylation, glycosylation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, sulfation, and transfer-RNA mediated additions of amino acids to 10 proteins such as arginylation and ubiquitination.

The ADAMTS-N proteins are immunogenic and, thus, are useful for preparing antibodies. Such antibodies are useful for identifying and diagnosing disorders which are associated with decreased expression or activity or increased expression of an ADAMTS-N protein. The 15 ADAMTS-N protein may also be useful for treating such disorder.

Diseases involving enhanced or depressed proteolyisis of the core proteins of the extracellular may involve enhanced expression or activity or decreased expression or activity of one or more ADAMTS-N proteins. Thus, ADAMTS-N proteins may be used to identify drugs,

20 polypeptides, auto-antibodies, or other natural compounds which bind to an ADAMTS-N protein with sufficient affinity to block or facilitate its activity. The activity of the ADAMTS-N protein is assayed in the presence and the absence of the putative inhibitor or facilitator using any of a variety of protease assays known in the

25 art. In general, the activity of the ADAMTS-N protein is assayed through the use of a peptide or protein substrate having a known or putative cleavage site for the ADAMTS-N protein. To detect cleavage or to monitor the extent of cleavage, the substrate is tagged in a manner which provides a detectable signal upon cleavage. For

side of the cleavage site and with a fluorescence-quenching group on the opposite side of the cleavage site. Upon cleavage by the substrate, quenching is eliminated and a detectable signal is produced. Alternatively, the substrate is tagged with a colorimetric leaving group that more strongly absorbs upon cleavage. Agents which block ADAMTS-N-catalyzed cleavage of a protein substrate may be administered to a subject to block proteolysis of the corresponding protein substrate.

ADAMTS-R1 Protein

The present invention also relates to a protein, referred to hereinafter as "ADAMTS-R1". From its amino to its carboxyl terminus, ADAMTS-R1 comprises a signal peptide sequence, a TS1 module, a cysteine-rich domain, a spacer domain, and three TS1 modules. Thus, ADAMTS-R1 has a structure which is related to or similar to an 15 ADAMTS-N protein, but which lacks a catalytic domain and a disintegrin-like domain. In one embodiment, ADAMTS-R1, protein comprises amino acid 1 through amino acid 525 of the amino acid sequence, SEQ ID NO:22, shown in Fig. 11. Such protein has a 30-40% overall sequence identity with similar regions of the ADAMTS-N 20 proteins. The ADAMTS-R1 proteins also encompass variants of the amino acid sequence shown in Fig. 11 and fusion proteins which contain the amino acid sequence shown in Fig. 11 or a variant thereof. On the basis of its domain organization, it is expected that ADAMTS-R1 can bind to extracellular matrix or cell surface 25 molecules, including ADAMTS-N substrates. Thus, it is expected that ADAMTS-R1 can be used as an cell-matrix or cell-cell adhesion molecule or an ADAMTS-N competitive inhibitor. The ADAMTS-R1 proteins are also useful for preparing antibodies. Such antibodies are useful for identifying tissues where ADAMTS-R1 is expressed and 30 for diagnosing disorders which are associated with decreased

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The present invention also provides isolated polynucleotides

expression or increased expression of. an ADAMTS-R1 protein.

Polynucleotides

which encode the mammalian ADAMTS-N proteins and the mammalian

5 ADAMTS-R1 protein. Figure 1 shows one embodiment of a
polynucleotide, SEQ ID NO: 1, which encodes the full-length mouse

ADAMTS-5 protein. Figure 2 shows one embodiment of a polynucleotide;

SEQ ID NO: 3, which encodes a partial human ADAMTS-5 protein. Figure

3 shows one embodiment of a polynucleotide; SEQ ID NO: 5, which

- 10 encodes a full-length human ADAMTS-6 protein. Figure 4 shows one embodiment of a polynucleotide; SEQ ID NO: 7, which encodes a full-length human ADAMTS-7 protein. Figure 5 shows one embodiment of a polynucleotide; SEQ ID NO: 9, which encodes a full-length mouse ADAMTS-8 protein. Figure 6 shows one embodiment of a polynucleotide;
- 15 SEQ ID NO: 11, which encodes a partial human ADAMTS-8 protein.

 Figure 7 shows one embodiment of a polynucleotide; SEQ ID NO: 13,

 which encodes a full-length human ADAMTS-9 protein. Figure 8 shows

 one embodiment of a polynucleotide; SEQ ID NO: 15, which encodes a

 partial ADAMTS-9 protein. Figure 9 shows one embodiment of a
- 20 polynucleotide; SEQ ID NO: 17, which encodes a full-length human ADAMTS-10 protein. Figure 10 shows one embodiment of a polynucleotide; SEQ ID NO: 19, which encodes a partial mouse ADAMTS-10 protein. Figure 11 shows one embodiment of a polynucleotide; SEQ ID NO: 21, which encodes a full-length ADAMTS-R1 protein.
- Due to the known degeneracy of the genetic code wherein more than one codon can encode the same amino acid, a DNA sequence may vary from that shown in SEQ ID NO: 1 and still encode an ADAMTS-5 protein having the amino acid sequence of SEQ ID NO: 2. Similarly, a DNA sequence may vary from that shown in SEQ ID NO:5, and still encode an ADAMTS-6 protein having the amino acid sequence set forth

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in SEQ ID NO:6. Similarly a DNA sequence may vary from that shown in SEQ ID NOS: 7, 9, 11, and 13, and still encode the amino acid sequences shown in SEQ ID NOS: 8, 10, 12, and 14, respectively. Such variant DNA sequence may result from silent mutations, such as for example those that occur during PCR amplification or from deliberate mutagenesis of a native sequence.

The present polynucleotides also encompass polynucleotides having sequences that are capable of hybridizing to the nucleotide sequences of FIGS 1 - 11 under stringent conditions, preferably 10 highly stringent conditions. Hybridization conditions are based on the melting temperature™ of the nucleic acid binding complex or probe, as described in Berger and Kimmel (1987) Guide to Molecular Cloning Techniques, Methods in Enzymology, vol 152, Academic Press. The term "stringent conditions, as used herein, is the "stringency" 15 which occurs within a range from about Tm-5 (5° below the melting temperature of the probe) to about 20° C below Tm. As used herein "highly stringent" conditions employ at least 0.2 x SSC buffer and at least 65° C. As recognized in the art, stringency conditions can be attained by varying a number of factors such as the length and 20 nature, i.e., DNA or RNA, of the probe; the length and nature of the target sequence, the concentration of the salts and other components, such as formamide, dextran sulfate, and polyethylene glycol, of the hybridization solution. All of these factors may be varied to generate conditions of stringency which are equivalent to the 25 conditions listed above.

The present polynucleotides also encompasses alleles of the ADAMTS-N and ADAMTS-R1 encoding sequences. As used herein, an allele or allelic sequence is an alternative form of an ADAMTS-N or ADAMTS-R1 encoding sequence which is present at the same gene locus. The 30 allele may result from one or more mutations in the ADAMTS-N or

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ADAMTS-R1 encoding sequence. Such mutations typically arise from natural addition, deletion of substitution of nucleotides in the open reading frame sequences. Any gene which encodes an ADAMTS-N protein or ADAMTS-RI protein may have none, one, or several allelic forms.

5 Such alleles are identified using conventional techniques, such as

5 Such alleles are identified using conventional techniques, such as for example screening libraries with probes having sequences identical to or complementary with one or more ADAMTS-N polynucleotides.

The present polynucleotides also encompass altered

10 polynucleotides which encode ADAMTS-N proteins, ADAMTS-R1 proteins, and variants thereof. Such alterations include deletions, additions, or substitutions. Such alterations may produce a silent change and result in an ADAMTS-N protein having the same amino acid sequence as the ADAMTS-N protein encoded by the unaltered polynucleotide. Such alterations may produce a nucleotide sequence possessing nonnaturally occurring codons. For example, codons preferred by a particular prokaryotic or eucaryotic host may be incorporated into the nucleotide sequences showing Figures 1 -11 to increase the rate of expression of the proteins encoded by such sequences. Such 20 alterations may also introduce new restriction sites into the sequence or result in the production of an ADAMTS-N or ADAMTS-RI variant. Typically, such alterations are accomplished using sitedirected mutagenesis.

The polynucleotides are useful for producing ADAMTS-N or

25 ADAMTS-R1 proteins. For example, an RNA molecule encoding an ADAMTSN protein is used in a cell-free translation systems to prepare such
protein. Alternatively, a DNA molecule encoding an ADAMTS-N protein
is introduced into an expression vector and used to transform cells.
Suitable expression vectors include for example chromosomal,

30 nonchromosomal and synthetic DNA sequences, e.g., derivatives of

SV40, bacterial plasmids, phage DNAs; yeast plasmids, vectors derived from combinations of plasmids and phage DNAs, viral DNA such as vaccinia, adenovirus, fowl pox virus, pseudorabies, baculovirus, and retrovirus. The DNA sequence is introduced into the expression 5 vector by 5 conventional procedures.

Accordingly, the present invention also relates to recombinant constructs comprising one or more of the present polynucleotide sequences. Suitable constructs include, for example, vectors, such as a plasmid, phagemid, or viral vector, into which a sequence that, 10 encodes an ADAMTS-N protein or an ADAMTS-R1 protein has been inserted. In the expression vector, the DNA sequence which encodes the ADAMTS-N protein is operatively linked to an expression control sequence, i.e., a promoter, which directs mRNA synthesis. Representative examples of such promoters, include the LTR or SV40 15 promoter, the E. coli lac or trp, the phage lambda PL promoter and other promoters known to control expression of genes in prokaryotic or eukaryotic cells or in viruses. The promoter may also be the natural promoter of the ADAMTS-N encoding sequence. The expression vector, preferably, also contains a ribosome binding site for 20 translation initiation and a transcription terminator. Preferably, the recombinant expression vectors also include an origin of replication and a selectable marker, such as for example, the ampicillin resistance gene of E. coli to permit selection of transformed cells, i.e. cells that are expressing the heterologous 25 DNA sequences. The polynucleotide sequence encoding the ADAMTS-N protein is incorporated into the vector in frame with translation initiation and termination sequences.

The polynucleotides encoding an ADAMTS-N or ADAMTS-R1 protein are used to express recombinant protein using techniques well known 30 in the art. Such techniques are described in Sambrook, J. et al.

(1989) Molecular Cloning A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y. and Ausubel, F. M. et al. (1989) Cuurent Protocols in Molecular Biology, John Wile & Sons, New York, NY.

Polynucleotides encoding an ADAMTS-N or ADAMTS-R1 protein may

5 also be used for diagnostic purposes. The polynucleotides may be

used to detect and quantify ADAMTS-N or ADAMTS-R1 gene transcripts in

biopsied tissues in which enhanced expression or reduced expression

of the corresponding ADAMTS-N or ADAMTS-RI gene is correlated with a

disease. The diagnostic assay may be used to determine whether

10 expression is absent, present, or altered and to determine whether

certain therapeutic agents modulate expression of the corresponding

ADAMTS-N or ADAMTS-R1 gene.

Also encompassed by the present invention, are single stranded polynucleotides, hereinafter referred to as antisense

- and RNA sequences which encode the ADAMTS-N or ADAMTS-R1 proteins.

 The term complementary as used herein refers to the natural binding of the polynucleotides under permissive salt and 5 temperature conditions by base pairing.
- The present invention also encompasses oligonucleotides that are used as primers in polyrnerase chain reaction (PCR) technologies to amplify transcripts of the genes which encode the ADAMTS-N and ADAMTSR-1 proteins or portions of such transcripts. Preferably, the primers comprise 18-30 nucleotides, more preferably 19-25
- 25 nucleotides. Preferably, the primers have a G+C content of 40% or greater. Such oligonucleotides are at least 98% complementary with a portion of the DNA strand, i.e., the sense strand, which encodes the respective ADAM-TS family protein or a portion of its corresponding antisense strand. Preferably, the primer has at least 99%
- 30 complementarity, more preferably 100% complementarity, with such

sense strand or its corresponding antisense strand. Primers which are which have 100% complementarity with the antisense strand of a double-stranded DNA molecule which encodes an ADAMTS-N protein have a sequence which is identical to a sequence contained within the sense 5 strand. The identity of primers which are 15 nucleotides in length and have full complementarity with a portion of the antisense strand of a double-stranded DNA molecule which encodes the ADAMTS-N protein is determined using the nucleotide sequences, shown in FIG I - 11 and described by the general formula a-b; where a is any integer between 10 I and the position number of the nucleotide which is located 15 residues upstream of the 3' end of the sense or antisense strand of the cDNA sequences shown in FIG 1 -11; where b is equal to a+14; and where both a and b correspond to the positions of nucleotide residues

The present invention also encompasses oligonucleotides that are useful as hybridization probes for for isolating and identifying cDNA clones and genomic clones encoding the ADAMTS-N or ADAMTS-R1 protein or allelic forms thereof. Such hybridization probes are also useful for detecting transcripts of the genes which encode the ADAMTS-N family proteins or for mapping of the genes which encode the ADAMTS-N proteins Preferably, such oligonucleotides comprise at least 210 nucleotides, more preferably at least 230, most preferably from about 210 to 280 nucleotides. Such hybridization probes have a sequence which is at least 90% complementary with a sequence 25 contained within the sense strand of a DNA molecule which encodes an ADAMTS-N protein or ADAMTS-R1 protein or with a sequence contained within its corresponding antisense strand. Such hybridization probes

bind to the sense strand under stringent conditions. The term

"stringent conditions" as used herein is the binding which occurs

30 within a range from about Tin 5'C (5'C below the melting temperature

Tm of the probe) to about 20°C to 25°C below Tm. The probes are used in Northern assays to detect transcripts of ADAMTS-N homologous genes and in Southern assays to detect ADAMTS-N homologous genes. The identity of probes which are 200 nucleotides 5 in length and have 5 full complementarity with a portion of the antisense strand of a double-stranded DNA molecule which encodes the ADAMTS-N protein is determined using the nucleotide sequences shown in FIG 1 - 10 and described by the general formula a-b; where a is any integer between I and the position number of the nucleotide which is located 200 .

10 residues upstream of the 3' end of the sense or antisense strand of the cDNA sequences shown in FIG 1 -10; b is equal to a +200; and where both a and b correspond to the positions of nucleotide residues of the cDNA sequences shown in FIG 1-10.

Such probes or primers are also useful for identifying tissues 15 or cells in which the corresponding ADAMTS-N or ADAMTS-R1 gene is preferentially expressed either constitutively or at particular state of tissue differentiation or development or in disease states. Expression of the ADAMTS-N or ADAMTS-R1 gene in a particular tissue or group of cells is determined using conventional procedures 20 including, but not limited to, Northern analysis, in situ hybridization to RNA or RT-PCR amplification. Isolated polynucleotides encoding an ADAMTS-N or ADAMTS-R1 protein are also useful as chromosome markers to map linked gene positions, to identify chromosomal aberrations such as translocations, inversions 25 and trisomies, to compare with endogenous DNA sequences in patients to identify potential genetic disorders, and as probes to hybridize and thus discover novel, related DNA sequences. For use in such studies and assays, the probes may be labeled with radioisotopes, fluorescent labels, or enzymatic labels. The assays include, but are 30 not limited to, Southern blot, in situ hybridization to DNA in cells

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and chromosomes, PCR, and allele specific hybridization.

Antibodies

In another aspect, the present invention relates to antibodies which are specific for and bind to the ADAMTS-5 protein, the ADAMTS-6 5 protein, the ADAMTS-7 protein, the ADAMTS-8 protein, the ADAMTS-9 protein, the ADAMTS-10 protein, or the ADAMTS-R1 protein. Such antibodies are useful research tools for identifying *tissues that contain elevated levels of the respective protein and for purifying the respective protein from cell or tissue extracts, medium of 10 cultured cells, or partially purified preparations of intracellular and extracellular proteins by affinity chromatography. Such antibodies are also useful for identifying and diagnosing diseases associated with elevated or reduced levels of an ADAMTS-N protein or ADAMTS-R1 protein. Such antibodies are also useful for monitoring 15 the effect of therapeutic agents on the synthesis and secretion of ADAMTS-N proteins by cells in vitro and in vivo. Such antibodies may also be employed in procedures, such as co-immunoprecipitation and co-affinity chromatography, for identifying other proteins, activators and inhibitors which bind to an ADAMTS-N or ADAMTS-R1 20 protein.

The present invention also provides a method for detecting an ADAMTS-N or ADAMTS-R1 protein, in a bodily sample from a patient using antibodies immunospecific for an ADAMTS-N or ADAMTS-R1 protein. The method comprises contacting the antibody with a sample taken from the patient; and assaying for the formation of a complex between the antibody and the corresponding ADAMTS-N or ADAMTS-R1 protein present in the sample. The sample may be a tissue or a biological fluid, including but not limited to whole blood, serum, synovial fluid, stool, urine, cerebrospinal fluid, semen, diagnostic washes from trachea, stomach and other bowel segments, tissue biopsies or excised

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tissue, cells obtained from swabs and smears. To monitor changes in expression of the ADAMTS-N protein during fetal development and pregnancy, it is preferred that the sample be amniotic fluid. To monitor changes in expression of the ADAMTS-N protein during joint 5 disorders, the preferred sample is synovial fluid. To monitor changes in expression of ADAMTS-N proteins during cancer, the preferred samples include, but are not limited to, serum, body fluids, or biopsy tissue. To monitor changes in expression of ADAMTS-N proteins during inflammation the preferred samples include; 10 but are not limited to, serum, body fluids, or biopsy tissue.

The sample may be untreated, or subjected to precipitation; fractionation, separation, or purification before combining with the anti-ADAMTS-N protein antibody. For ease of detection, it is

preferred that isolated proteins from the sample be attached to

15 a substrate such as. a column, plastic dish, matrix, or membrane,

preferably nitrocellulose. Preferably, the detection method employs
an enzyme-linked immunosorbent assay (ELISA) or a Western immunoblot

procedure.

Interactions between an ADAMTS-N protein in the sample and the

20 corresponding anti ADAMTS-N antibody are detected by radiometric,
colorimetric, or fluorometric means, size separation, or
precipitation. Preferably, detection of the antibody-ADAMTS-N
protein complex is by addition of a secondary antibody that is
coupled to a detectable tag, such as for example, an enzyme,

25 fluorophore, or chromophore. Formation of the complex is indicative
of the presence of the ADAMTS-N protein in the test sample. Thus,
the method is used to determine whether there is a decrease or
increase in the levels of the ADAMTS-N protein in a test sample as
compared to levels of the ADAMTS-N protein in a control sample and to

30 quantify the amount of the ADAMTS-N protein in the test sample.

Deviation between control and test values establishes the parameters for diagnosing the disease.

Preparing the ADAMTS-N proteins and the ADAMTS-R1 protein

The ADAMTS-N proteins and the ADAMT-SR1 protein may be produced 5 by conventional peptide synthesizers. The ADAMTS-N proteins and the ADAMTS-R1 protein may also be produced using cell-free translationsystems and RNA molecules derived from DNA constructs that encode an ADAMTS-N protein or an ADAMTS-RI protein. Alternatively, ADAMTS-N proteins are made by transfecting host cells with expression 10 vectors that comprise a DNA sequence that encodes the respective ADAMTS-N protein and then inducing expression of the protein in the host. cells. For recombinant production, recombinant constructs comprising one or more of the sequences which encode the ADAMTS-N protein or a variant thereof are introduced into host cells by 15 conventional methods such as calcium phosphate transfection, DEAEdextran mediated transfection, transvection, microinjection, cationic lipid-mediated transfection, electroporation, transduction, scrape lading, ballistic introduction or infection.

The ADAMTS-N protein and the ADAMTS-R1 protein may be expressed 20 in suitable host cells, such as for example, mammalian cells, yeast, bacteria, insect cells or other cells under the control of appropriate promoters using conventional techniques. Suitable hosts include, but are not limited to, E. coli, P. pastoris, Cos cells and 293 HEK cells. Following transformation of the suitable host strain and growth of the host strain to an appropriate cell density, the cells are harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification of the ADAMTS-N protein or the ADAMTS-R1 protein.

Conventional procedures for isolating recombinant proteins from 30 transformed host cells, such as isolation by initial extraction from

cell pellets or from cell culture medium, followed by salting-out, and one or more chromatography steps, including aqueous ion exchange chromatography, size exclusion chromatography steps, and high performance liquid chromatography (HPLC), and affinity chromatography 5 may be used to isolate the recombinant ADAMTS-N protein or ADAMTS R1 protein

Preparation of Antibodies

The ADAMTS-N proteins, and variants thereof are used as immunogens to produce antibodies immunospecific for one or more

10 ADAMTS-N protein. The term "immunospecific" means the antibodies have substantially greater affinity for one or more ADAMTS-N protein than for other proteins. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, and Fab fragments.

- Antibodies are also prepared using an oligopeptide having a sequence which is identical to a portion of the amino acid sequence of an ADAMTS-N protein. Preferably the oligopeptide has an amino acid sequence of at least five amino acids, and more preferably, at least 10 amino acids that are identical to a portion of the amino
- 20 acid sequence of an ADAMTS-N protein. Such peptides are conventionally fused with those of another protein such as keyhole limpet hemocyanin and antibody produced against the chimeric molecule. One preferred oligopeptide for preparing an antibody to mouse ADAMTS-5 has the sequence (C)HIKVRQFKAKDQTRF, SEQ ID NO: 30.
- 25 Another preferred oligopeptide for preparing an antibody to ADAMTS-5 is CEAKNGYQSDAKGVKTFVEWVPKYAG, SEQ ID NO: 3 1. One preferred oligopeptide for preparing an antibody to ADAMTS-6 has the sequence SVSIERFVETLVVADK(C), SEQ ID NO:23. One preferred oligopeptide for preparing an antibody to ADAMTS-7 has the sequence
- 30 (C) EVAEAANFLALRSEDPEKY, SEQ ID NO:24. One preferred oligopeptide for

preparing an antibody to ADAMTS-8 has the sequence CVKEDVENPKAVVDGDWGP, SEQ ID NO:25. One preferred oligopeptide for preparing an antibody to ADAMTS-9 has the sequence QHPFQNEDYRPRSASPSRTH, SEQ ID NO:26. Another preferred oligopeptide

- 5 for preparing an antibody to ADAMTS-9 has the sequence
 PQNCKEVKRLKGASEDGEYF, SEQ ID NO:27. One preferred oligopeptide for
 preparing an antibody for ADAMTS-R1 has the sequence QELEEGAAVSEEPS,
 SEQ ID NO:28. Another preferred oligopeptide for preparing an
 antibody for ADAMTS-R1 has the sequence YYPENIKPKPKLQE; SEQ ID NO:29.
- 10 Polyclonal antibodies are generated using conventional techniques by administering the ADAMTS-N protein or achimeric molecule to a host animal. Depending on the host species, various adjuvants may be used to increase immunological response. Among adjuvants used in humans, Bacilli Calmette-Guerin (BCG), and
- 15 Corynebacterium parvum. are especially preferable. Conventional protocols are also used to collect blood from the immunized animals and to isolate the serum and or the IgG fraction from the blood.

For preparation of monoclonal antibodies, conventional hybridoma techniques are used. Such antibodies are produced by continuous cell lines in culture. Suitable techniques for preparing monoclonal antibodies include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV hybridoma technique.

Various immunoassays may be used for screening to identify

25 antibodies having the desired specificity. These include protocols which. involve competitive binding or immunoradiometric assays and typically involve the measurement of complex formation between the respective ADAMTS-N protein and the antibody.

Polynucleotides that encode ADAMTS-N proteins

30 Polynucleotides comprising sequences encoding an ADAMTS-N

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protein or an ADAMTS-R1 protein may be synthesized in whole or in part using chemical methods. Polynucleotides which encode an ADAMTS-N protein, particularly alleles of the genes which encode the ADAMTS-N protein, may be obtained by screening a genomic library or 5 cDNA library with a probe comprising sequences identical or complementary to the sequences shown in Figures 1 - 10 or with antibodies immunospecific for a ADAMTS-N protein to identify clones containing such polynucleotide.

Example 1 ADAMTS-512 protein

A cDNA encoding mouse ADAMTS-5 protein was obtained using IMAGE 10 Clone 569515, purchased from Research Genetics, Huntsville, Alabama and 7 day old mouse embryo cDNA library from Clontech, Palo Alto, CA. A cDNA encoding human ADAMTS-5 protein was obtained using IMAGE Clone 345484 purchased from Research Genetics, Huntsville, Alabama 15 and a human fetal brain cDNA from Clontech. The clone inserts were sequenced in their entirety. Using oligonucleotide primers based on the sequences at the ends of the. clone inserts as template, successive rounds of RACE (Rapid Amplification of cDNA Ends) by PCR was performed at 5' and 3 ends. RACE primers were generated 50-200 20 bp from the ends of the sequences so that the contiguity of RACE clones with the I.M.A.G.E. clone could be clearly established. A single round of 5' and 3' 20 RACE sufficed for cloning of the entire coding sequence of the mouse ADAMTS-5 protein and part of the catalytic zinc binding site through to the stop codon of the human 25 ADAMTS-5 protein. Primers were designed with calculated Tm>72°C and RACE was performed with nested primers for each amplification. PCR used the Advantage PCR reagents (Clontech, Palo Alto, CA); the polymerase mix contained both Taq polymerase as well as proofreading polymerase to minimize PCR errors and employed "hot-start" PCR for 30 optimal efficiency. RACE used the following "touch-down" cycle

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conditions; 95°C for 1 minute followed by 5 cycles of 95°C for 0.5 minutes, 72°C for 5 minutes, then 5 cycles of 95°C for 0.5 minutes, 70°C for 5 minutes and 20 cycles of 95°C for 0.5 minutes, 68°C for 5 minutes. The PCR products were analyzed by Southern blotting, 5 initially using [\alpha^{32}P]-dCTP labeled.

Hybridizing bands were ligated into pGEM-T Easy (Promega,
Madison, WI) and individual clones were selected by another round of
Southern analysis. Automated nucleotide sequencing of both strands
of each clone were done at the Molecular Biotechnology Core of the 10

Lerner Research Institute, Cleveland Clinic Foundation and nucleotide
sequence data were analyzed using the DNAStar software. By
integration of the overlapping sequences thus obtained, a contiguous
nucleotide sequence was determined. The nucleotide sequence of the
mouse ADAMTS-5 cDNA and the predicted amino acid sequence of the
15 protein encoded by this cDNA are shown in Fig. 1. The nucleotide
sequence of the human ADAMTS-5 cDNA and the predicted partial amino
acid sequence of the protein encoded by this cDNA are shown in Fig.
2.

The predicted molecular mass (Mr) of the mature ADAMTS-5

20 protein is 73717.50 daltons. It is expected that the actual Mr of the active ADAMTS-5 protein is different due to post-translational modification, which could potentially increase the Mr. The predicted domain organization of ADAMTS-5 protein relative to the cloned cDNA is shown in Figure 12. The pro-domain of the full-length mouse

25 ADAMTS-5 protein has 3 consensus cleavage signals for furin. The most carboxyl-terminal furin cleavage site in ADAMTS-5 predicts the processing site for generation of the mature protein The catalytic domain of the ADAMTS-5 protein contains eight cysteine residues and a reprolysin -zinc binding signature sequence, i.e., HEIGHLLGLSHD.

30 Five cysteine residues are upstream of the zinc binding sequence,

· while three residues are downstream, an arrangement that is shared with other ADAMTS members. The zinc binding signature is followed by a "Met-turn". The catalytic domain is followed by a domain with 35% similarity to snake venom disintegrins. The disintegrin domain 5 contains eight cysteine residues. The first TS repeat contains 52 residues and is followed by a conserved cysteine-rich sequence termed the cysteine-rich domain, designated "CRD", to distinguish it from the cysteine-free spacer domain. The CRD contains ten conserved cysteines and demonstrates high sequence homology with the CRD of -10 other ADAMTS-N proteins. The spacer domain of mouse ADAMTS-5 is 158 amino acids in length and is followed by a second TS module. ADAMTS-5 contains three potential glycosylation sites in the mature protease one of which is just upstream of the start of the spacer domain and the second lies within the spacer domain and the third is near the 15 start of the disintegrin domain. The human ADAMTS-5 protein and the mouse ADAMTS-5 protein have 96% sequence identity. ADAMTS-5 bears 46% sequence identity to ADAMTS-4 (KIAA0688), which is characterized as being involved in catabolism of aggrecan core protein in arthritis and 60% identity to ADAMTS-1 which is involved in inflammation.

20 Example 2 ADAMTS-6

30 within the ORF.

length ADAMTS-6 protein was obtained using IMAGE clone 742630, which encodes EST AA400393, and a human fetal brain cDNA from Clontech.

RACE was performed as described above in Example 1. The I.M.A.G.E.

25 clone 742630 contained an ORF flanked by consensus splice sequences, indicating the presence of introns. Two successive rounds of RACE at the 5' end and a single round of RACE at the 3' end provided the complete coding sequence of ADAMTS-6. The putative ATG codon is within a Kozak consensus sequence and encodes the first methionine

The nucleotide sequence of a human cDNA encoding the full-

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The nucleotide sequence of the ADAMTS-6 DNA is shown in Fig. 3 The predicted amino acid sequence, SEQ ID NO:6, of the ADAMTS-6 protein is also shown in Fig. 3. The predicted Mr of the fulllength, unprocessed ADAMTS-6 protein is 97,115 daltons., and the 5 predicted Mr of the mature ADAMTS-6 protein is 68412.10 daltons. The domain organization of the ADAMTS-6 protein is shown in Fig. 12. The pro-domain of the full-length ADAMTS-6 protein has one consensus cleavage signal for furin. The catalytic domain of the ADAMTS-6 contains six cysteine residues and the reprolysin -zinc binding 10 signature sequence, HEIVHNFGMNHD, which is followed by a "Met-tum". The catalytic domain is followed by a domain with 35% similarity to disintegrins. The disintegrin domain contains snake venom eight cysteine residues. The first TS repeat contains 52 residues and is followed by a conserve CRD sequence which contains ten 15 conserved cysteines and demonstrates high sequence homology with the CRD of other ADAMTS proteins. The spacer domain of ADAMTS-6 is 127 amino acids in length and is followed by a second TS module. ADAMTS-6 contains four potential glycosylation sites within the pyo-domain and two in the mature protease one of which is in the cysteine rich 20 domain and the other of which is in the spacer domain. ADAMTS-6 bears 46% sequence identity to ADAMTS-1, which is involved in inflammation.

Example 3 ADAMTS-7.

The nucleotide sequence of a cDNA encoding an ADAMTS-7 protein

25 was obtained using IMAGE clone 272098, which encodes EST N4.8032, and
a human fetal brain cDNA from Clontech. RACE was performed as
described above in Example 1. The I.M.A.G.E. clone 272098 encoded a
putative pre-pro region and was extended in the 3'-direction by two
successive rounds of RACE. A typical signal peptide sequence lies

30 downstream of the first methionine in the translated ORF. This

methionine codon lies within a satisfactory Kozak consensus for translation initiation.

The nucleotide sequence of the ADAMTS-7 cDNA is shown in Fig.

4. The predicted amino acid sequence, SEQ ID NO: 8, of the ADAMTS-7

- 5 protein is also shown in Fig. 4. The predicted Mr of the hilllength, unprocessed ADAMTS-7 protein is 116,607 daltons, and the
 predicted Mr of the mature ADAMTS-7 protein is 84005 daltons. The
 domain organization of the ADAMTS-7 protein is shown in Fig. 12. The
 pro-domain of the full-length ADAMTS-7 protein has one consensus

 10 cleavage signal for furin. The catalytic domain of the ADAMTS-7
 protein contains eight cysteine residues and the reprolysin-zinc
 binding signature sequence, HELGHSFGIQHD, which is followed by a

 "Met-tum". The catalytic domain is followed by a domain with 30%
 similarity to snake venom disintegrins The disintegrin domain
 15 contains eight cysteine residues. The first TS repeat contains 52
 residues and is followed by a conserved CRD sequence which contains
 ten conserved cysteines. The spacer domain of ADAMTS-7 is 221 amino
 acids in length and is followed by a second TS module and a short
 sequence containing two cysteine residues. ADAMTS-7 contains three
- 20 potential glycosylation sites within the mature protease; one of which is just upstream of the spacer domain and one of which is within the spacer domain. ADAMTS-7 bears 35 % sequence identity to ADAMTS-1, which is characterized as being involved in inflammation and 32% identity to ADAMTS-2 which is a procollagen processing

25 enzyme.

Example 4: ADAMTS-8

The nucleotide sequence of a cDNA encoding a full-length, mouse ADAMTS-8 protein was obtained using IMAGE clone 1260693, which encodes EST AA855532, and a mouse embryo cDNA from Clonetech. The 30 nucleotide sequence of a cDNA encoding a partial ADAMTS-8 human

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protein was obtained using IMAGE clone 2119838, which encodes EST A1400905, and a human fetal brain cDNA library from Clontech. RACE was performed, as described above in Example 1. The nucleotide sequence of the cDNA encoding the full-length ADAMTS-8 mouse protein and the amino acid sequence of such protein is shown in Fig. 5. The nucleotide sequence of the cDNA encoding the partial ADAMTS-8 human protein and the amino acid sequence of such protein is shown in Fig. 6.

The predicted Mr of the full-length, unprocessed ADAMTS-8 mouse 10 protein is 1260693 daltons, and the predicted Mr of the mature ADAMTS-8 protein is 68412.10 daltons. The pro domain of the fulllength ADAMTS-8 protein has one consensus cleavage signal for furing The catalytic domain contains eight cysteine residues and the reprolysm-zinc binding signature sequence, HELGHVLSMPHD, which is 15 followed by a "Met-turn". The catalytic domain is followed by a domain with 20-30% similarity to snake venom disintegrins. The disintegrin-like domain contains eight cysteine residues. The first TS repeat is followed by a conserved CRD sequence which contains 10 conserved cysteines. The spacer domain of ADAMTS-8 is 146 amino 20 acids in length and is followed by a second TS module. The ADAMTS-8 protein contains 4 potential glycosylation sites within the mature protease: one is in the cysteine-rich domain; one is in the catalytic domain; and two are in the disintegrin-like domain. ADAMTS-8 bears 46% sequence identity to ADAMTS-1 and 42% identity to 25 ADAMTS-4.

Example 5: ADAMTS-9
The nucleotide sequence of a cDNA encoding a full-length, human
ADAMTS-9 protein was obtained using IMAGE clone 646675, which encodes
EST AA205581, and a human fetal brain cDNA from Clonetech. The
30 micleotide sequence of a cDNA encoding a partial ADAMTS-9 mouse

protein was obtained using IMAGE clone 535663, which encodes EST AAl 06215, and a mouse cDNA library obtained from Clonetech. RACE was performed as described above in Example 1. The nucleotide sequence of the cDNA encoding the full-length ADAMTS-9 human proteinand the amino acid sequence of such protein is shown in Fig.6. The nucleotide sequence of the cDNA encoding the partial ADAMTS-9 mouse protein and the amino acid sequence of such protein is shown in Fig. 7.

The predicted Mr of the mature human ADAMTS-9 protein is

10 189777.20 daltons. The prodomain of the predicted ADAMTS-9 protein
has 3 consensus cleavage signal for furin. The catalytic domain of
the ADAMTS-9 contains eight cysteine residues and the reprolysin zinc binding signature sequence, HELGHVFNMPHD, which is followed by a
"Met-turn". The catalytic domain is followed by a domain with 25-30%

15 similarity to snake venom disintegrins The disintegrin domain
contains eight cysteine residues. The first TS repeat contains is
followed by a conserved CRD sequence which. contains 10 conserved
cysteines. The spacer domain of ADAMTS-9 is 124 amino acids in
length and is followed by 14 additional TS modules and a C-terminal
20 domain. The ADAMTS-9 protein contains 6 potential glycosylation
sites within the mature protease: one in the spacer domain, one in
TSP 1 -7, one in TSPI-8, and 3 in the C-terminal domain. The ADAMTS9 bears 44% sequence identity to ADAMTS-4.

Example 6: ADAMTS-10

The nucleotide sequence of a cDNA encoding a fall-length
ADAMTS- 10 protein was obtained using IMAGE clone 110403, which
encodes EST AA588434, and a human fetal brain cDNA from Clonetech.
The nucleotide sequence of a cDNA encoding a partial, mouse ADAMTS-10
protein was obtained using IMAGE clone 1077653, which encodes EST

30 AA822090, and a mouse embryo cDNA library from Clonetech. RACE was

performed as described above in Example 1. The nucleotide sequence of the human ADAMTS-10 cDNA and the predicted amino acid sequence, SEQ ID 18, of the human ADAMTS-10 protein encoded by such DNA is shown in Fig. 9. The nucleotide sequence of the cDNA encoding the partial mouse ADAMTS-10 protein and the amino acid sequence of such protein is shown in Fig. 10.

The predicted Mr of the mature ADAMTS-10 protein is 95238

daltons. The pro-domain of the full-length ADAMTS-10 protein has no consensus cleavage signal for furin. The catalytic domain of the 10 ADAMTS-10 contains eight cysteine residues and the reprolysin-zinc binding signature sequence, HEIGHTFGMNHD, which is followed by a "Met-turn". The catalytic domain is followed by a domain with 30% similarity to snake venom disintegrins. The disintegrin-like domain contains eight cysteine residues. The first TS repeat is followed by a conserved CRD sequence which contains 8 conserved cysteines. The spacer domain of ADAMTS-10 is followed by 4 additional TS modules and a Kunitz domain. The ADAMTS-10 protein contains 2 potential glycosylation sites within the mature protease: one in the catalytic domain, and one in the TS 1-3 domain. ADAMTS-10 bears approximately 40% sequence identity to ADAM-TS1, which is characterized as being involved in inflammation.

Comparison of the ADAMTS-N Proteins.

As shown in Figure 11, the ADAMTS-5. ADAMTS-6, and ADAMTS-7

proteins share a common domain organization. From amino to carboxyl

25 termini, they are as follows:

1. A pre-pro region. A typical signal sequence of variable length is followed by a putative pro-region of variable length but demonstrating short stretches of sequence identity. Three cysteine residues are, predicted within each novel pro-domain, of which the
30 most C-terminal is an "asymmetric" cysteine lying within a sequence

context similar to the cysteine "switch" of the MMPs. All three novel cDNAs predict consensus cleavage signals for furin, three in the case of ADAMTS-5, and one each in the case of ADAMTS-6 and ADAMTS-7. The most carboxyl-terminal furin cleavage site in ADAMTS-5 predicts the processing site for generation of the mature protease. The amino terminus of the mature proteins is predicted to start at the residue immediately following the cleavage sites.

- 2. A catalytic domain. The catalytic domains are very similar to each other and contain eight cysteine residues and a typical
- 10 reprolysin-type zinc binding signature followed by a "Met-turn".

 Five cysteine residues are upstream of the zinc binding sequence,
 while three residues are downstream, an arrangement that is shared
 with other ADAMTS members. The methionine of the met-turn is not at
 a constant distance from the zinc-binding signature, but in all three
 15 novel proteases, a constant cysteine residue is present in that
 interval.
- 3. A disintegrin-like domain. The catalytic domain is followed by a domain of 60-90 residues with 35-45% similarity to snake venom disintegrins, but without the canonical cysteine arrangement seen in 20 the latter. This disintegrin-like domain is of comparable length in ADAMTS-5 and ADAMTS-7, it is considerably shorter in ADAMTS-6.
- 4. A TS module. The first TS repeat is very similar in all three novel proteases and very similar to the first TS repeat of other ADAMTSs. It contains the same number of residues (fifty-two) in all 25 three novel proteins.
 - 5. The cysteine-rich domain. This TS domain is followed by a conserved cysteine-rich sequence termed the cysteine-rich domain (CRD).
- 6. The spacer domain. This domain is of variable length, in all 30 ADAMTSs and lacks the sequence landmarks so characteristic of all the

other domains. It shows the least homology of all the domains.

7. A C-terminal TS module. The sequence of the second TS module is more variant between the members of the ADAMTS family than the first TS module, despite the conservation of the number and spacing 5 of cysteine residues.

Overall, the predicted mature forms of these proteases show 20-30% similarity to each other and to ADAMTS1-4 although this may be considerably higher or lower for individual domains as described above.

- ADAMTS-9 and ADAM-TS10 contain all the domains present in ADAMTS-5 through ADAMTS-8. In addition, ADAMTS-9 and ADAMTS-10 contain the following domains:
- A. ADAMTS-9: After the c-terminal TS1 domain which is present in ADAMTS5-8, ADAMTS-9 contains 13 additional and homologous 15 TS11 domains, thus, ADAMTS-9 contains a total of 15 TS1 domains, of which 14 are adjacent to each other in the c-terminal half of the molecule. The 15th TS1 domain from the N-terminus is followed by a unique c-terminal domain which does not possess recognizable domain structure and contains 196 residues including 9 cysteine residues.
- B. ADAMTS-10: After the c-terminal TS1 domain which is present in ADAMTS 8, ADAMTS-10 contains 3 additional and homologous TS1 domains, thus, that ADAMTS-10 contains a total of 5 TS1 domains, of which 4 are adjacent to each other in the c-terminal half of the molecule. The 5th TS 1 domain from the N-terminus is followed by an additional 47 amino acid residues including six (6) cysteine residues. These 47 residues have sequence similarity of 30%-40% to the c-terminus of pro-hormone convertase 5 and 6, and to the Kunitz family of inhibitors.
- Northern Analysis

 Mouse embryo northern blots and multiple tissue northern blots

-35-

from human and mouse tissues (Clontech, Palo Alto, CA) were hybridized to the $\{\alpha^{32}P\}$ -dCTP labeled inserts of I.M.A.G.E. clones as per the manufacturer's recommendations followed by autoradiographic exposure for 3-7 days.

In situ hybridization used cryosections of mouse embryos of gestational age 8.5 days and 10.5 days. Embryos were collected with the inclusion of the surrounding uterus and fixed overnight in 4% paraformaldehyde. Sense and anti-sense probes continuously labeled with digoxigenin-UTP (Boehringer-Mannheim, Indianapolis, IN) were 10 transcribed with T7 and T3 RNA polymerases, respectively, using as template a 63 0 bp EcoRI-Sacl fragment from the Adamts-5 clone 569515 (Fig. 14) cloned into pBluescript SK+ (Stratagene, La Jolla, CA). In situ hybridization was done essentially as previously described in Apte, et al. (1997) J. Biol. Chem. 272:2551-25517, which is 15 specifically incorporated herein by reference, except that sections were predigested with proteinase K (Boehringer-Mannheim, Indianapolis, IN) at a lower, concentration (1 -5 μ g/ml) than reported in Apte, et al.. Bound, digoxigenin-labeled probe was detected using an alkaline phosphatase tagged anti-digoxigenin 20 antibody (Boehringer-Mannheim, Indianapolis, IN) and nuclei were

Specific hybridization of the antisense Adamts-5 probe to sections of 8.5 day-old mouse embryos was obtained, whereas only low background staining was noted with the control sense probe. Staining 25 was uniform throughout the 8.5 day old embryos. In addition, there was labeling of mRNA in trophoblastic cells lining the uterine cavity as well as in the developing placenta (Fig. 14). The decidual reaction within the uterus also showed upregulation of Adamts-5 mRNA relative to the negative controls. In sections from 10.5 day old 30 embryos, labeling was widespread but less intense compared to the 8.5

counterstained with methyl green.

day-old embryo. Labeled cells were seen in mesenchyme and somites as well as in the neural tube and developing hindgut. Northern analysis also indicated that mRNA encoding ADAMTS-5 was present in human placenta but was barely detectable in adult lung, heart, brain, 5 liver, skeletal muscle, kidney and pancreas.

Northern analysis showed undetectable expression of Adamts-6 during mouse embryo development. Northern analysis indicated that mRNA encoding ADAMTS-6 was present in human placenta but was barely detectable in adult lung, heart, brain, liver, skeletal 10 muscle, kidney and pancreas. Adamts-7 was expressed at low levels throughout mouse development. In adult human tissues examined with human cDNA probes, ADAMTS-7 mRNA was found in all tissues examined, i.e. in lung, heart, brain, liver, skeletal muscle, kidney, pancreas and placenta. The sizes of the mRNA species recognized by the probes 15 varied. ADAMTS-5 mRNA was approximately 10 kbp in size in human tissue. The most prominent Adamts-5 species was estimated at 7.5 kbp together with additional bands at 10 kbp and 4.5 kbp. The lone mRNA species detected by ADAMTS-6 probe was approximately 8.5 kbp, whereas the most common mRNA species detected by ADAMTS-7 probe 5 was 5 kbp 20 in size with an additional species seen at 7 kbp in skeletal muscle.

In mouse, ADAMTS-8 is expressed during fetal development (days 7, 11, 15, 17) and in adult mouse lung and heart with an mRNA size of approximately 3.8 kbp. In adult human tissue, ADAMTS-8 is expressed in lung and brain but not in heart, muscle, kidney, colon or thymus.

25 The mRNA size is 3.8 kbp.

ADAMTS-9 is expressed in lung, ovary placenta, heart, brain, muscle, kidney and pancreas with a mRNA size of 8 kb. In addition, kidney and ovary contain additional transcripts of size 3 kb and 4.4 kb respectively. These additional transcripts may represent 30 alternatively spliced or short forms of ADAMTS9.

ADAMTS-10 is expressed in thymus, prostate, testis, ovary, small intestine, colon, peripheral blood leukocytes, heart, brain, placenta, lung, liver, muscle, kidney and pancreas, as well as in many cell lines such as A549, HeLa and K562. There are two 5 transcripts of 5 kb and 8kb present in all tissues.

Example 7: ADAMTS-R1

The nucleotide sequence of a cDNA encoding a full-length ADAMTS-R1 protein was obtained using IMAGE clone 752797 which encodes EST AA, and a human fetal brain cDNA from Clontech. RACE was 10 performed as described above in Example 1. The nucleotide sequence, SEQ ID NO:21, of the ADAMTS-R1 cDNA and the predicted amino acid sequence, SEQ ID NO:22, of the ADAMTS-R1 protein encoded by such DNA is shown in Fig. 11.

The predicted Mr of the full-length, unprocessed ADAMTS-R1 15 protein is 58358.20 daltons. The domain organization of the ADAMTS-10 protein is shown in Fig. 15. In contrast to the ADAMTS-N proteins of examples 1-6, ADAMTS-R1 protein does not have a prometalloprotease or disintegrin-like domain or a consensus cleavage signal for furin. ADAMTS-R1 has a signal (pre) peptide which is 20 followed by a first TS module and a conserved CRD sequence which contains 10 conserved cysteines. The spacer domain of ADAMTS-R1 is 115 amino acids in length and is followed by 3 additional TS modules and a short sequence of 33 amino acids. The ADAMTS-R1 protein contains one potential glycosylation sites which is in the spacer 25 domain. ADAMTS-R1 bears 30-40% sequence identity to ADAMTS1 and ADAMTS4 in the related domains. ADAMTS-R1 mRNA is present in human heart, brain, kidney, muscle, lung, placenta, testis, ovary, colon, intestine, and prostate. There are three transcripts of 2.5 kb, 4.7 kb and 6.5 kbp present in all such tissues. In mouse, expression is 30 seen in skeletal muscle, and the transcript size is 6.5 kb.

Although certain embodiments of this invention have been shown and described, various adaptations and modifications can be made without departing from the scope of the invention as defined in the appended claims.

CLAIMS

- 1. An isolated mammalian protein selected from the group consisting of an ADAMTS-5 protein an ADAMTS-6 protein, an ADAMTS-7 protein, an ADAMTS-8 protein, an ADAMTS-9 protein, an ADAMTS-10 protein, and an ADAMTS-R1 protein.
- The isolated mammalian protein of claim 1 wherein said protein 2. comprises an amino acid sequence which is at least 95% identical to a sequence selected from the group consisting of: amino acid 262 through amino acid 930 of SEQ ID NO:2; amino / 10 acid 1 through amino acid 518 of SEQ ID NO:4; amino acid 245 through amino acid 860 of SEQ ID NO:6; amino acid 233 through amino acid 997 of SEQ ID NO:8; amino acid 229 through amino acid 905 of SEQ ID NO:10; amino acid 1 through amino acid 245 of SEQ ID NO:12; amino acid 236 through amino acid 1882 of SEQ 15 ID NO:14; amino acid 1 through amino acid 874 of SEO ID NO:16; amino acid 212 through amino acid 1081 of SEQ ID NO:18; amino acid 1 through amino acid 450 of SEQ ID NO:20; and amino acid 1 through amino acid 547 of SEQ ID NO:22.
- The isolated protein of claim 2 wherein said amino acid
 sequence further comprises a prepropeptide sequence at the amino terminus thereof.
 - 4. The isolated protein of claim 1 wherein said protein is a human ADAMTS-5 protein or a mouse ADAMTS-5 protein.
- The isolated protein of claim 1 wherein said protein is a humanADAMTS-6 protein.
 - 6. The isolated protein of claim 1 wherein said protein is a human ADAMTS-7 protein.
 - 7. The isolated protein of claim 1 wherein said protein is a mouse ADAMTS-8 or a human ADAMTS-8 protein.
- 30 8. The isolated protein of claim 1 wherein said protein is a human

10

- ADAMTS-9 or a mouse ADAMTS-9 protein.
- 9. The isolated protein of claim 1 wherein said protein is a human ADAMTS-10 or a mouse ADAMTS-10 protein.
- 10. The isolated protein of claim 1 wherein said protein is a human

 ADAMTS-R1 protein.
 - 11. An isolated polynucleotide comprising a sequence which encodes a mammalian protein selected from the group consisting of an ADAMTS-5 protein, an ADAMTS-6 protein, an ADAMTS-7 protein, an ADAMTS-8 protein, an ADAMTS-9 protein, an ADAMTS-10 protein, and an ADAMTS-R1 protein.
- The isolated polynucleotide of claim 11 wherein said protein 12. comprises an amino acid sequence which is at least 95% identical to a sequence selected from the group consisting of: amino acid 262 through amino acid 930 of SEQ ID NO:2; amino acid 1 through amino acid 518 of SEQ ID NO:4; amino acid 245 15 through amino acid 860 of SEQ ID NO:6; amino acid 233 through amino acid 997 of SEQ ID NO:8; amino acid 229 through amino acid 905 of SEQ ID NO:10; amino acid 1 through amino acid 245 of SEQ ID NO:12; amino acid 236 through amino acid 1882 of SEQ ID NO:14; amino acid 1 through amino acid 874 of SEQ ID NO:16; 20 amino acid 212 through amino acid 1081 of SEQ ID NO:18; amino acid 1 through amino acid 450 of SEQ ID NO:20, and amino acid 1 through amino acid 547 of SEQ ID NO:22.
- 13. The isolated polynucleotide of claim 11 wherein said nucleotide
 25 sequence encodes a protein having a signal sequence at the
 amino terminus thereof.
 - 14. The isolated polynucleotide of claim 11 wherein said polynucleotide comprises a sequence selected from the group consisting of: nucleotide 800 through nucleotide 2810 of SEQ ID NO:1 of an allelic variant thereof; nucleotide 1 through

30

10

nucleotide 1519 of SEQ ID NO:3 or an allelic variant thereof; nucleotide 754 through nucleotide 2602 of SEQ ID NO:5 or an allelic variant thereof; nucleotide 708 through nucleotide 3003 of SEQ ID NO:7 or an allelic variant thereof; nucleotide 962 through nucleotide 2992 of SEQ ID NO:9 or an allelic variant thereof; nucleotide 1 through nucleotide 739 of SEQ ID NO:11 or an allelic variant thereof; nucleotide 708 through nucleotide 5648 of SEQ ID NO:13 or an allelic variant thereof; nucleotide 1 through nucleotide 2625 of SEQ ID NO:15 or an allelic variant thereof; nucleotide 634 through nucleotide 3243 of SEQ ID NO:17 or an allelic variant thereof; nucleotide 1 through nucleotide 1642 of SEQ ID NO:19 or an allelic variant thereof; and nucleotide 51 through nucleotide 1625 of SEQ ID NO:21 or an allelic variant thereof.

- 15 15. The isolated polynucleotide of claim 11 wherein said polynucleotide hybridizes under stringent conditions to a nucleic acid molecule comprising a sequence complementary to the protein encoding sequence of SEQ ID NO:1; SEQ ID NO:3; SEQ ID NO:5; SEQ ID NO:7; SEQ ID NO:9; SEQ ID NO:11; SEQ ID NO:13;

 20 SEQ ID NO:15; SEQ ID NO:17; SEQ ID NO:19; or SEQ ID NO:21.
 - 16. An isolated polynucleotide having a sequence which is complementary to the protein encoding sequence of the

polynucleotide of claim 11.

- 17. An expression vector comprising a polynucleotide of claim 11.
- 25 18. A host cell transformed or transfected with an expression vector of claim 17.
 - 19. A method for producing an ADAMTS-N protein or an ADAMTS-R1 protein, said method comprising the steps of
- (a) culturing a host cell of claim 18 under conditions30 suitable for expression of an ADAMTS-N protein or an ADAMTS-R1

1. 4 5. 5 V 1. 45 . 7 S.

protein; and

- (b) recovering said ADAMTS-N protein or said ADAMTS-R1 protein from the host cell culture.
- 20. An antibody that binds to a protein selected from the group

 5 consisting of an ADAMTS-5 protein, an ADAMTS-6 protein, an

 ADAMTS-7 protein, an ADAMTS-8 protein, an ADAMTS-9 protein, an

 ADAMTS-10 protein and an ADAMTS-R1 protein.
- 21. An oligopeptide for producing an antibody that binds to an ADAMTS-N protein or an ADAMTS-R1 protein wherein said

 10 oligopeptide has a sequence selected from the group consisting of:
 - a) SVSIERFVETLVVADK, SEQ ID NO:23;
 - b) EVAEAANFLALRSEDPDKY, SEQ ID NO:24;
 - c) VKEDVENPKAVVDGDWGP, SEQ ID NO:25;
- d) QHPFQNEDYRPRSASPSRTH, SEQ ID NO:26;
 - e) PQNCKEVKRLKGASEDGEYF, SEQ ID NO:27;
 - f) OELEEGAAVSEEPS, SEQ ID NO:28;
 - g) YYPENIKPKPKLQE; SEQ ID NO:29;
 - h) HIKVRQFKAKDQTRF; and
- 20 i) CEAKNGYQSDAKGVKTFVEWVPKYAG, SEQ ID NO:30.

Fig. 1

FEATURES

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Fig. 2

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ar grande

Fig. 3

FEATURES

Location/Qualifiers

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Fig. 3 (con't)

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Last Callers

Fig. 4

FEATURES

source

Location/Qualifiers

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PVFSWHYGPWTKCTVTCGRGEKWGRHSPTCRGLVSGQGHWLQLPAHCWATTGLEVCFS
EPQFSICEMRLAIALCPRPAGRVHG*

BASE COUNT 584 a 1041 c 1003 g 590 t ORIGIN

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Fig. 5A

10 20 30 40 50 60 70
tagggcgactgcacgggacgccgcggaggacgcgcgctcgcgggccccggggcgccacgtgctcgagttctg 70
ctaggttggctggcgcaggaggggctgcgcgatccagaggggccgccaggggaccgccgcgccacgt 140
gccgctagccgagtcggcctccccatccgattgatcatttttcctggacagagcgacccggccgcctcgg 210
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CTCCGCGACCCCACCACCGCGTGCCGCCCCTCCTGCTGCTGCTGCTGCTGCCGCCG
360 370 380 390 400 410 420
TCGTCTCCGGAGCCCCGGCGGGGCCGGGAACCGGGGCGCGGGGCCTCGGAGCTAGTGGTGCCCACGCGGTT 420
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CCTGACGCCAGCTTCCTGCGCCGGAATTCAAGATCGAGCGCCTCGGGGGCTCGAGCGCGGGCGG
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710 720 730 740 750 760 770
GCIGGGGACICCCTGGACCAGCCTCATCGCCTGCAGCGCTGGGGGCCCGGGACAGCGCCGGGAAGACCCCCG 770
GECTICGCTGCCGCCGAAGTTTTCCCCCTCCAAGGACTGGAGTGGGAGGTGGAGATGGGTAATGGGCA 840
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1060 1070 1080 1090 1100 1110 1120
<u> </u>
CCTCACGGTGATGTCAATGGCAGCCCGAATCTACAAGCACCCGAGCATCAGGAACTCCGTCAACCTTGTG 1120
GIGGIGAAAGIGCIAATAGIGGAAAAAGAAGATGGGGCCCGGAAGIGICCGACAACGGGGGGCTCACAC 1190
TCCCCAACTTCTCCACCTCCCAACCCCCTTTCAACAACCCCAGTCACCCCCCCC
TGCCATCTTGTTCACCAGACAGAACTTCTGTGGGAAGGGAGAGCAGTGTGACACCCTGGGGATGGCAGAC 1330
GITGGCACCATCIGIGACCCCGACAAGAGCIGCTCAGIGATCAAGGATGAGGGACIGCAGGCAGCCTACA 1400
1410 1420 1430 1440 1450 1460 1470
CCCIGGCCCATGAGCTAGGGCACGTTCTCAGCATGCCCCCATGATGATTCTAAGCCCTGTGTGAGATTGTT 1470
TEGECCCATGEGCAAGTACCACATGATGGCGCCATTCTTCATCCACGTGAACAAGACGCTGCCCTGGTCT 1540
CCCTGCAGTGCTGTCTACCTCACAGAGCTCCTGGATGATGGTCACGGAGATTGTCTTCTGGATGCCCCCA 1610
CCTCGGTTCTGCCCCTCCCCACAGGCCTCCCGGGCCACAGCACCCTCTACGAGCTGGACCAGCAGTGCAA 1680
GCAGATCTTTGGGCCTGATTTCCGACACTGCCCCAACACCTCTGTGGGAGGACATCTGTGTCCAGCTCTGT 1750

9/54 Fig. 5A (con't)

1766	`	1770	4500	4500			
1760		1770	1780	1790	1800	1810	1820
TITLL TITLL							
GCCCGTCATCG							
CACCCTGTGGC							
GGCTGTGGTAG							
ATACAATTCTC							
GAGTCAAGTAC						-	
2110		2120	2130	2140	2150	2160	2170
TEACA ATTACK							
TGAGAAATATA	AIGCCIA	CAACCACAC	CIGACCIGGAT	GGGAATTICC	TGCAGTGGGT	CCCCAAGTAI	TCA 2170
OGAGTGTCCCC	ACCEALEAC ACCERTAGE	CGATGCAAC	CIGITITICA	GAGCCCGTCC	GAGGAGIGAG	TICAAAGIGI	TTG 2240
AAGCTAAGGTG							
TAAGGCTGGCT							
GCACTGCCTG							
2460		2470	2480	2490	2500	2510	2520
management.							
TCCCAGCTGGT	JCCACAA	ACATIGATO	TGAAACAGCG	GAGICACCCA	LGGGGTCAGGA	ACGACGCAG	CTA 2520
CCTGGCGCTGA	AGACAGC	CAATGGGCA	GIACCIGCIC	AATGGTAACC	TGGCCATCTC	TGCCATAGAG	CAA 2590
GACATCTTGGT							
TCCAGGCCCTG							
CAGATATACCT					ATAGCAAGGA	AAGAGCAACC	ACC 2800
2810		2820	2830	2840	2850	2860	2870
				1111111 1		uluulu	
AACATCATTCA							
GAGGTAGCTGG	AGCGGC	GGACIGIGO	AATGCAGGGA	CCCCTCAGGI	CAGGCCTCTG	ACACCIGIGA	TGA 2940
GGCTCTGAAAC	-1GAGGA	TGCCAAGCC	CIGIGGAAGO	CAGCCGIGIC	CCCTCtgate	cccttggtgg	aaa 3010
tetettagget	alggat	ttgggctac	tggtgtaaca	gacaaaggtc	ccctccaagg	tgatactaca	tat 3080
caagatggcac		caggeett	ctattactac	aaccccttgg	gtactaccta	attcataagg	aag 3150
3160	•	3170	3180	3190	3200	3210	3220
agagaagaggg							
agaagtcggga							
uttgcaaagga	tttgcaaaggactagcaaagctaaatgaaaaagaagaatttttttt						
aatetaceteacagegggaaaaateagtatacaagaggtataaggecaggtgttggcagtgaaegceaa 3430 agcaagetecataggtatetecaagetatetteagaaatgteegtggetgtttteagtattaaaatetgt 3500							
aycaagctcca	caggtat	ctccaagct	atcttcagaa	atgtccgtgg	ctgttttcag	tattaaaatc	tgt 3500

10/54

Fig. 5A (con't)

3510	3520	3530	3540	3550	3560 LL	3570	
tgtctaaaagg	gcagcagtgtcca ttcaagtatttato	tcacagggtta	atagaaagcc	acttttctcag	ggctgccacct	gctgg 3570	

MOUSE HDAM 758 10 MLRDPTTTGWPPLLLLLLQLPPPPLVCGAPAGPGTGAOAS 40 ELVVPTRLPGSASELAFHLSAFGQGFVLRLAPDASFLAPE 80 FKIERLGGSSAAAGGEPGLRGCFFSGIVNGERESLAAMSC 120 VAGWSGSFILLAGEEFTIQPQGAGDSLDQPHRLQRWGPGQR 160 REDPGLAAAEVFPLPQGLEWEVEMGNGQGQERSDNEEDRK 200 210 220 230 N-terminus of mature QDKEGLLKETEDSRKVPPPFGSKTRSKRFVSEARFVETLL 240 VADASMAAFYGIDLONHILIVMSMAARIYKHPSIRNSVNL 280 WVKVLIVEKERWGPEVSDNGGLTLRNFCSWQRRFNKPSD 320 RHPEHYDTAILFIRONFOGKGEOCDILGMADVGTICDPDK 360 SCSVIKDEGLQAAYTLAHELGHVLSMPHDDSKPCVRLFGP 400 410 420 430 440 MGKYHMMAPFFIHVNKFLPWSPCSAVYLTELLDDGHGDCL 440 LDAPTSVLPLPTGLPCHSTLYELDOOCKOIFGPDFRHCPN 480 TSVEDICVQLCARHRDSDEPICHTKNGSLLWADGTPCGPG 520 8 4 HLCLDGSCVLKEDVENPKAVVDGDAGPARPAGOCSRTCGG 560 GIQFSNRECDNPMPQNGGRFCLGERVKYQSCNTEECPPNG 600 610 620 630 640 KSFREQQCEKYNAYNH DLDGNFLQWYPKYSGVSPRDRCK 640 LFCRARGRSEFKVFEAKVIDGILCGPDILSICVRGQCVKA 680 10 CY GCDHVVNSPKKLDKCGVCGGKGTACRKISGSFTPFSYGYN 720 spacer ~146aa DIVTIPAGATNIDVKORSHPGVRNDGSYLALKTANGOYLL 760 NGNLAISAIEQDILVKGTTLKYSGSMATTLERLQSFQALPE 800 810 820 830 840 PLTVQLLTVSGEVFPPKVRYTFFVPNDMDFSVQNSKERAT 840 INTIQSLPSAEWVLGDWSECPSTCRGSWORRTVECRDPSG 880 QASDICDEALKPEDAKPCGSQPCPL 905

Fig. 6A

	0.0-0.	A.	545 A 14 C	ANAm	T(-8	(HUMAN).	
				1101111	.5 0		
10	20	30	40				
CGAGGGCAGAAGGCGC							•
GGCCACGAGTAGGAC							
TICGIGGAGACGCIGC							
CCTTCTACGGGGCCG						•	•
AATGICIGIGGCAGC	CGAATCTAC	AAGCACCC	CAGCATC 2	200			
210	220	230	240				•
mulmulmul	لتبيطيين	سسلسب	حليتين				
AAGAATTCCATCAAC	TGATGGTGG	TAAAÀGTG	TIGATOG 2	240		•	
TAGAAGATGAAAAAT	3GGGCCCAGA	GGTGTCCG/	ACAATGG 2	280		•*	•
GGGCTTACACTGCG	CAACTTCTGC	AACTGGCAG	CCCCCT 3	320	•		
TTCAACCAGCCCAGC	3ACCGCCACC	CAGAGCAC	TACGACA	360			
CGGCCATCCTGCTCA	CAGACAGAA	CITCIGIG	GCAGGA 4	100		•	**
410	420	430	440				***
	ليسلسيا	ستأسب	للبيبا			-,	
GGGGCTGTGTGACAC	creecicie	GCAGACAT(OGGGACC 4	14 0			
ATTTGTGACCCCAAC							
AGGGGCTCCAGGCGG							
GCACGTCCTCAGCAT	GCCCCACGAC	GACTCCAA	SCOCTEC!	560			
ACACGGCTCTTCGGG							
610	620	630	640				
CACCGCTGTTCGTCC				640			
CCCCTGCAGCGCCAT							
TGGATCCATTTCAAG	_						
TAAAGIGIGATCITA							

HUMAN ADAM-TSE CATALYTIC DOMAIN

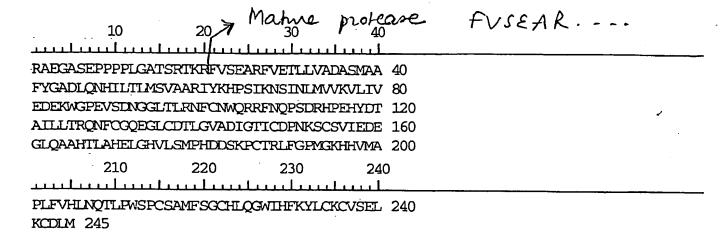


Fig. 6B

Fig. 7A

Fig. 7A (con't)

1760	1770	1780	1790	1800	1810	1820
لسيلسلسل	سيبيب	ىلىسىلىن	ىلىسىلىنى		ىلىسىلىپ	<u> </u>
CTGCAACACGGAGCC	ATGTCTCAAGC	'AGAAGCGAGA	CTTCCGAGAT	GAACAGIGIG	CICACITIGA	ACGGG 1820
AAGCATTTTAACATC	AACGGICIGCI	TCCCAATGIG	CGCTGGGTCC	CIAAATACAG	TGGAATTCTC	ATGA 1890
AGGACCGGTGCAAGT.	IGITCIGCAGA	GTGGCAGGGA	ACACAGCCTA	CIATCAGCII	CGAGACAGAG	FIGAT 1960
AGATGGAACICCTIG	IGGCCAGGACA	CAAATGATAT	CIGIGICCAG	GCCTTTGCC	GGCAAGCTGG	ATGC 2030
GATCATGITTTAAAC	ICAAAAGCCCCC	GAGAGATAAA	TGCCCCGTTT	GIGGIGGCGA	TAATICTICA	ATGCA 2100
2110	2120	2130	2140	2150	2160	2170
استلسلسا	بلينيلين	<u> بلينيان،</u>	بليبيلين	بلينيلين		
AAACAGTGGCAGGAAG	CATTTAATACA	GTACATTATG	GTTACAATAC	TGTGGTCCGA	ATTCCAGCTC	GTGC 2170
TACCAATATTGATGT	GCGCACCACA	GTTTCTCAGG	GGAAACAGAC	GATGACAACT	ACTTAGCTTI	ATCA 2240
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GGAATGCTGTGGTAG	AGTACAGTGGG	TCCGAGACTG	CCGTAGAAAG	AATTAACTCA	ACAGATOGCA	TTGA 2380
GCAAGAACTTTTGCT	CAGGITTIGI	CGGTGGGAAA	GITGIACAAC	CCCGATGTAC	GCTATTCTTI	CAAT 2450
2460	2470	2480	2490	2500	2510	2520
	ىلىنىلىن	بلينيلين	بلينتيلين	بالتسليب	بسيست	ــــــــــــــــــــــــــــــــــــــ
ATTCCAATTGAAGATA	AAACCTCAGCA	GITITACTGG	AACAGTCATG	GGCCATGGCA	AGCATGCAGI	AAAC 2520
CCTGCCAAGGGGAAC	GAAACGAAAA	CITGITTCCA	CCAGGGAATC	TGATCAGCTT	ACIGITICIO	ATCA 2590
AAGATGCGATCGGCT	CCCCAGCCTC	GACACATTAC	TGAACCCTGT	GGTACAGGCT	GTGACCTGAC	GTGG 2660
CATGTTGCCAGCAGG	AGTGAATGTAG	TICCCCAGIGI	GCTTGCGTT	'ACCGCACATT	GGACATCTAC	TGTG 2730
CCAAATATAGCAGGC	IGGATGGGAAG	ACTGAGAAGG	TTGATGATGG	TTTTTGCAGC	AGCCATCCCA	AACC 2800
2810	2820	2830	2840	2850	2860	2870
استاستاستا	بالبنياليين		بليتتليين			
AAGCAACCGTGAAAA	ATGCTCAGGGG	AATGTAACAC	GGGIGGCIGG	CCTATTCTC	CCTGGACTGA	ATGT 2870
TCAAAAAGCTGTGAC	GTGGGACCCA	GAGGAGAAGG	GCTATTTGTG	TCAATACCCG	AAATGATGTA	CTGG 2940
ATGACAGCAAATGCAG	CACATCAAGAC	AAAGTTACCA	TTCAGAGGTG	CAGIGAGITC	CCTTGTCCAC	AGIG 3010
GAAATCTGGAGACTG	STCAGAGIGCI	TGGTCACCTG	TGGAAAAGGG	CATAAGCACC	GCCAGGICIC	GIGT 3080
CAGTITIGGIGAAGAT	CGATTAAATGA	TAGAATGTGT	GACCCTGAGA	CCAAGCCAAC	ATCTATGCAG	ACTT 3150
3160	3170	3180	3190	3200	3210	3220
استلسلسنا	بلينيلين	بليتبلين	بلينتلين	بليتيلين	بليينانين	
GTCAGCAGCCGGAATC	TICCATICCTIC	CAGGCGGGTC	CCTGGGTACA	GIGCAGIGIC	ACTIGIGGAC	AGGG 3220
ATACCAGCTAAGAGC	AGTGAAATGCA	TCATTGGGAC	TTATATGTCA	GTGGTAGATG	ACAATGACTO	TAAT 3290
GCAGCAACTAGACCA	ACTGATACCCA	GGACTGTGAA	TACCATCAT	GICATCCICC	CCCAGCIGCC	CCCGG 3360
AAACGAGGAGAAGCA	CATACAGIGCA	CCAAGAACCC	'AGTGGCGATT	TGGGTCTTGG	ACCCCATGCT	CAGC 3430
CACTTGTGGGAAAGG	PACCOGGATGA	GATACGICAG	CTCCCGAGAT	GAGAATGGCT	CIGIGGCIGA	ACGAG 3500

Fig. 7A (con't)

3510	3520	3530	3540	3550	3560	3570
لسيلسيلسي	لسيلس	لتبتليين	لتتبليين	التسليين	لمساسب	
AGIGCCIGIGCTACC	CTGCCTAGAC	CAGTGGCAAA	GGAAGAATGI	TCTGTGACAC	CCTGTGGGCA	ATGGA 3570
AGGCCTTGGACTGGA	CCTCTTGCTC	TGTGACCTGT	GGGCAAGGTA	GGGCAACCCG	CAAGTGATG	rgrgr 3640
CAACTACAGTGACCA	CGTGATCGAT	CCGAGTGAGT	GIGACCAGGA	TTATATCCCA	GAAACTGACC	AGGAC 3710
TGTTCCATGTCACCA	TGCCCTCAAA	GGACCCCAGA	CAGIGGCTTA	GCTCAGCACO	CCTTCCAAAA	TGAGG 3780
ACTATOGICCCOGGA	GCGCCAGCCC	CAGCCGCACC	CATGTGCTCG	KGTGGAAACCA	GIGGAGAACI	GGCCC 3,850
3860	3870	3880	3890	3900	3910	3920
لسيلسيلسي	ليبيليين	ليتقلين	لتتبليين	ليبتليب	ليستلسب	
CIGGGGAGCATGITC	CAGTACCIGI	GCTGGCGGAT	CCCAGCGGCC	TGITGITGTA	TGTCAGGATG	AAAAT 3920
GGATACACCGCAAAC	GACIGIGIGE	ACAGAATAAA	ACCIGATGAC	CAAAGAGCCT	GTGAATCCGG	CCCTT 3990
GTCCTCAGTGGGCTT	ATGGCAACTG	GGGAGAGTGC	ACTAAGCTGT	GIGGIGGAGG	CATAAGAACA	AGACT 4060
GGTGGTCTGTCAGCC	CICCAACGGI	GAACGGITTO	CAGATTIGAC	CIGIGAAATI	CTTGATAAAC	CTCCC 4130
GATCGIGAGCAGIGI	AACACACATO	CITGICCACA	CGACGCTGCA	TGGAGTACTG	GCCCTTGGAG	CICGI 4200
4210	4220	4230	4240	4250	4260	4270
لىنىلىنىلىنىل	ليسلسب	لسياس	ليتتبليني	muluul	لتستليين	
GPICIGICICITIGIC	XGTCGAGGGCA	TAAACAACGA	AATGITTACI	CCATGGCAAA	AGATGGAAGC	CATTT 4270
AGAAAGIGATTACTO	TAAGCACCTC	GCTAAGCCAC	ATGGGCACAC	GAAAGTGCCGA	GGAGGAAGAT	GCCCC 4340
AAATGGAAAGCTGG	CCTTCGAGTC	AGIGCICIGI	GICCIGIGG	CGAGGCGTAC	AGCAGAGGCA	TGTGG 4410
GCTGTCAGATCGGAZ	CACACAAAAT	ACCCAGAGAG	ACCGAGIGCA	ACCCATACAC	CAGACCGGAG	TCGGA 4480
ATGCGAATGCCAAGC	CCCACGGIGI	CCCCTTTACA	CTTGGAGGG	AGAGGAATGG	CAAGAATGCA	CCAAG 4550
4560	4570	4580	4590	4600	4610	4620
ليبتليبين	ليبيلينيا	لتتبليين	ليسلسن	لتسلسيا	لتسليب	
ACCTGCGGCGAAGGC	TCCAGGTACC	CAAGGIGGI	GIGIGIGGAT	IGACAACAAAA	ACGAGGIGCA	TGGGG 4620
CACGCTGTGACGTG	AGCAAGCGGCC	CGTGGACCGT	GAAAGCTGTA	AGTTTGCAACC	CTGCGAGTAT	GICIG 4690
GATCACAGGAGAAT	CICAGAGIC	YICAGIGACCI	GIGGAAAAG	CTACAAACAA	AGGCITGICI	CGIGC 4760
AGCGAGATITIACACC	COGGAAAGAG	ATTATGAATA	CAGCTACCA	AACCACCATCA	ACTGCCCAGG	CACGC 4830
AGCCCCCAGIGITC	CACCCCTGTT	ACCIGAGGGAC	Tecccieic.	CCCCACCIC	GAGAGIIGGC	AACTG 4900
4910	4920	4930	4940	4950	4960	4970
		ليبيليين	سيبليين	لتتتليييا	لتسليب	
GGGGAGCTGCTCAG:	referreres.	GITGGAGIGA	TCCAGAGAT	CIGIGCAAIG	ttaaccaatg	gaggac 4970
caacccagccactt	atoccacacto	gatetgaagee	cagaagaacg	aaaaacctgcc	gtaatgtcta	staact 5040
gtgagttaccccag	attocaago	aggtaaaaaga	acttaaaggtg	gccagtgaaga	itggtgaatat	effect 2110
gatgattagaggaa	agcttctgaag	gatattctgtg	geggggatge	actctgaccac	cccaaagagt	acgtg blev
acactggtgcatgg	agactctgag	atttctccga	aggtttatgg	gcacaggttac	cacaACCCAAC	CAGAAT 5250

Fig. 7A (con't)

	5260	5270	5280	5290	5300	5310	5320
للبينا	للسلسل	للسللسب	ليتتلين	للسلسل	ليبيليين	لتتبيلينيا	
GTCCC	TATAACGGGA	3CCGGCGCGA1	GACIGCCAA!	IGICGGAAGG?	ATTACACGGCC	CCTCCCTTT	rccag 5320
TTTTC	AGAAAATCAG	AATAGACCTG!	ACCAGCATGC/	AGATAATCACC	CACTGACTTAC	AGTITGCAAC	GACA 5390
AGCGA.	AGGACATOCO	FICCCITITIC	CACAGCCGC	GATICCTAC!	AGCGCTGCCAA	AGTGCCCACAC	EGGTC 5460
GITTI	AGCATCAACC.	TTATGGAACC	COCCUTOTOT	TAACTGAATC	TGCCAGATGC	ATATCACAA	3GGAA 5530
TTATG	CTGTCTCTGAG	CATCAAGAAGI	CGCCGGATGC	FIACCCGAGIC	CTACCGAAAI	GCCGTCGTTA	ACTGT 5600
	5610	5620	5630	5640	5650	5660	5670
<u> </u>							
GGAAAATGCACTCCATCCTCTGGTACTGGCCTGGAGGTGCGAGTTTTATAGCTAAGGTGCTTTGAAGAGG 5670							
AAGCC	ATTATOGATO	SATGAAGGATA	GTAATGCAAT	PACCICCACCI	TAATTIGGGI	GCATGIGIAT	GIGI 5740
GIGIG	IGITIGIGIG	GACTIGIATO	ETTGTGTGTC	FIAAATGTGTG	TACATATACA	TATATACA S	804

Fig. 7B

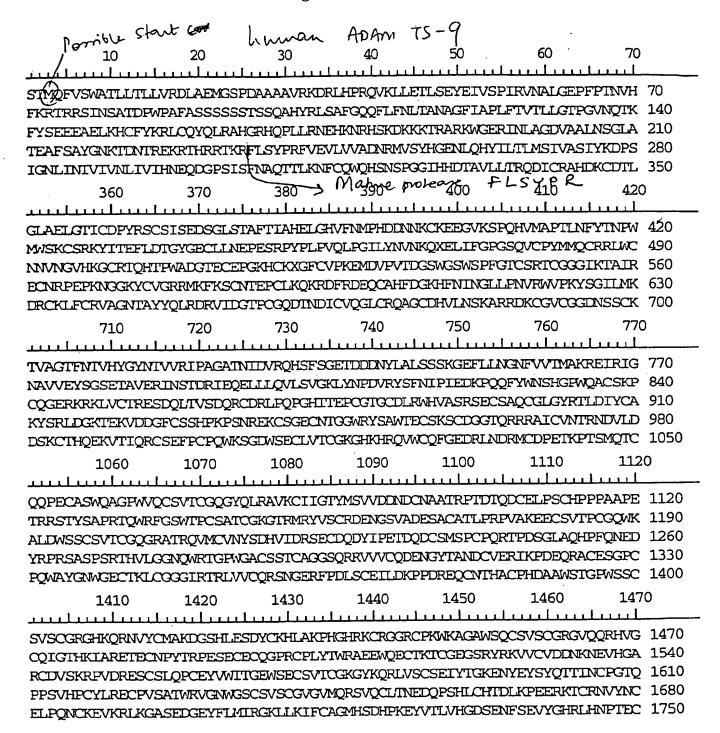


Fig. 7B (con't)

	1760	1770	1780	1790	1800	1810	1820
بلبين	بليبيليب	ليسلبب	ليتبلين	لتستلسب	لتستلينيا	لتسليب	
PYNGSF	RDDCQCRKDY	TAAGFSSFQ	KIRIDLTSMQ	IITTDLQFA	RTSEGHPVPFA	TAGDCYSAAF	KCPQGR 1820
FSINLY	/GTGLSLTESA	RWISQGNYA	VSDIKKSPDG	TRVVGKCGGY	CCKCTPSSGI	GLEVRVL.LF	CFEEE 1890
AIMDG.	RIVMQYLHLN	LGACVCVCV	FVCDLYACVC	KCVYIYIYT	1934		

Fig. 8

ORF=2 HTAVISLCSGMMGTFRSHDGDYFTEPLOSVDDQEDEEEON 40 mahne ADAMTS9 KPHITYRHSTPOREPSTGKHACATSELKNSHSKDKRKIRM 80 RKRRKRNSLADDVALLKSGLATKVLSGYSNOTNVTRDRWN 120 FLSYPRF ... HKRTKRFLSYPRFVEVMVVADHRMVLYHGANLQHYILILM 160 Mouse Apam-759 pout-al sequence (dee figure SIVASIYKDSSIGNLINIVIVNLVVIHNEQEGPYINFNAQ 200 TTLKNFCQWQHSKNYLGGIQHDTAVLVIREDICRAQDKCD 240 TLGLAELGTICDPYRSCSISEDSGLSTAFTIAHELGHVFN 280 MPHDDSNKCKEEGVKSPQHVMAPTLNFYINFWMWSKCSRK 320 YITEFLDIGYGECLLNEPASRTYPLPSQLPGLLYNVNKQC 360 ELIFGPGSQVCPYMMQCRRLWCNNVDGAHKGCRTQHTPWA 400 DGTBCEPGKHCKFGFCVPKEMBGPAIDGSWBGWSHFGTCS 440 RICGGGIKTAIRECNRPEPKNGGKYCVGRRMKFKSCNTEP 480 CMKQKRDFREEQCAHFDGKHFNINGLLPSVRWFPKYSGIL 520 MKDRCKLFCRVAGNTAYYQLRDRVIDGTPCGQDTNDICVQ 560 GLCRQAGCDHILNSKVRKDKCGICGGDNSSCKIVAGIFNI 600 VHYGYNIVVRIPAGATSIDVRQHSFSGKSEDDNYLALSNS 640 KGEFLLNGDFVVSMSKREVRVGSAVIEYSGSDNVVERLNC 680 TDRIEEELLLQVLSVGKLYNPDVRYSFNIPIEDKPQOFYW 720 NSHGPWQACSKPCQGERRRKLVCTRESDQLTVSDQRCDRL 760 POPGPVTEACGIDCDLRWHVASKSECSAQCGLGYRILDIH 800 CAKYSRMDGKTEKVDDSFCSSQPRPSNQEKCSGECSTGGW 840 RYSAWTECSRSCDGGTQRRRAICVNTRNDVLDDS 874

Created: Saturday, April 10, 1999 11:40 AM

Fig. 8 (con't)

360	370	380	390	400	410	420
لىسلىسلىسا	بسلسب	l	لتتبليين	سيبلس	لمبيليية	
ACAGATGGAACCACA	VAAAGAACCAA	ACCCITICIC.	ICCTACCCAC	CGITTGTAGA	EGIGATOGIC	GTGGC 420
TGACCACAGGATGGT	TTTATACCAC	GAGCAAACC.	ITCAACATTA	TATCITAACC	ITAATGTCCA	TIGTA 490
CCTTCTATCTATAA	GACTCAAGTA	TTGGAAATTT	TTATAATTAA	GITATIGIGA	ACTTAGTTGI	GATTC 560
ATAATGAACAGGAAC	GACCTTACATZ	AAATTTCAAT	3CCCAGACAA	CATTAAAGAA	CITTICCCAG	IGGCA 630
CCACTCAAAGAACT	CTTCCCTCCC	ATTCAGCACG	ACACAGCCGI	TCTGGTCACA	AGGGAAGATA'	ICIGC 700
710	720	730	740	750	760	770
لستلستست	لسسلسب	malaut	لىسلىس		Liui	
AGAGCTCAGGACAA						
GTTCCATTAGTGAAC	CACAGIGGGCIV	GAGCACAGCT.	TTCACAATAG	CICACGAGCI	EGGCCATGIG	ITTAA 840
TATGCCTCACGATG	CACCAATAAA	IGCAAAGAAG!	AAGGAGITAA	GAGTCCCCAG	CATGICATGG	CACCA 910
ACACTGAACTTCTAC	CACCAACCCCT	EGATGTOGTC	AAAGIGCAGI	CGGAAATACA'	ICACIGAGITI	CCTAG 980
ACACTGGGTACGGAC	AGIGCITCCI	GAATGAACCT	CATCCAGGA	CCTATCCTTTC	3CCTTCCCAA(CIGCC 1050
1060	1070	1080	1090	1100	1110	1120
لتتتليبيليين	لتستليين	لسبلس	لتسليب	لسطست	ليسلسن	ــــــــــــــــــــــــــــــــــــــ
CGGCCTTCTCTACAZ	CGTGAATAAA	CAATGIGAAC	IGATTTTTGG	SCCAGGCTCT	CAAGIGIGCC	CCTAT 1120
ATGATGCAGTGCAG	ACGGCTCTGGTV	CAATAATGI	GATGGAGCA	CACAAAGGCT	CAGGACTCA	GCACA 1190
CGCCCTGGGCAGATC	GAACCGAGIG	TGAGCCTGGA	AAGCACTGCA	AGTTTGGATT	rigigiiccc	AAAGA 1260
AATGGAGGCCCTCC	'AATTGATGGA'	TCCTGGGGAG	GITIGGAGCCA	CITIGGGACC	IGCICAAGAA	CGIGI 1330
GGAGGAGGCATCAA	ACAGCCATCA	GAGAGTGCAA	CAGACCAGAG	CCAAAAAATC	JIQQGAAGTA	CIGIG 1400
1410	1420	1430	1440	1450	1460	147 0
لسلسلسا	لسيلسا	للتنتليب	لتسلبين	لتتبيليين	لتبينليني	
TAGGAAGGAGAATG	AGTTCAAATC	CTGCAACACG	GAGCCCTGCA	TGAAGCAGAA	GCGAGACTTO	CGAGA 1470
GGAGCAGIGICCIC	ACTTTGATGGC	AAACACTTCA	ACATCAATGO	rerecreece	AGCGTACGCT	GGTTT 1540
CCTAAGTACAGCGG	ATTTTGATGA	AGGACCGGIG	CAAGITGITC	TGCAGAGTGG	CAGGAAACAC	ACCCT 1610
ACTACCAGCTCCGAC	CACAGAGIGAT	TGACGGAACC	CCTTGTGGCC	'AGGACACAAA'	IGACATCIGI	GICCA 1680
AGGCCTTTGCCGGCZ	AGCIGGAIGI	GATCATATIT	TAAACTCAAA	LCGTCCGGAAA	GATAAATGIG	GGATT 1750
1760	1770	1780	1790	1800	1810	1820
ليسلسلس	لسيلسا	لتتبليين	لبسلسي	ليتتلينن	ليتتليين	
TGTGGTGGAGATAA	TTCTTCATGCA	AAACAGTGGC	AGGAACATTT	AACACIGICC	ATTATGGTTA	CAATA 1820
CIGITGICCGAATIC	COGCIGGIGC	TACCAGCATI	GACGIGCGIC	AGCACAGCTI	CTCAGGGAAG	TCTGA 1890
GGATGACAACTACC	PAGCTTTATCA	AACAGTAAAG	GIGAATICCI	GCTAAATGGA	GACTITIGITG	TCTCC 1960
ATGTCCAAAAGGGAG	33100003166	GGAGCGCCGI	CATTGAGTAC	AGCGGATCGG	ACAATGTGGT	GGAAA 2030
GACTGAACTGTACG	GACCGTATCGA	GGAAGAACIT	CICCTICAGO	agrigicogi	GGGAAAGCTG	татаа 2100

Fig. 8 (con't)

	2110	2120	2130	2140	2150	2160	2170
عليتند	بليتينانين	لسبلس	ىلىبىلىن	بلينييلين	سلسسلس	ىلىنىلىن	
CCCAGA	TGTGCGGTAC	TCATTCAAT	ATTCCCATTGA	GGACAAACCI	CAGCAATITE	ACTGGAACAG	TCAC 2170
GGGCCG	TGGCAAGCAT	TGCAGCAAGC	CTCCCAAGC	GAGCOGAGAC	GAAAACTTGT	ITGCACCAGG	GAGT 2240
CTGATO	'AGCTAACCG	TTCTGATCA	AAGATGTGACC	GGCTGCCCCA	GCCAGGACCI	GICACTGAAG	CGIG 2310
CCCCAC	AGACTGTGAC	TTGAGGTGG	CACGITGCCAC	CAAGAGCGAA	TGCAGTGCCC	AGIGIGGITT	GGGC 2380
TACCGI	'ACTTTAGAC	ATCCACTGTG	CAAATACAGC	ACGATCGACG	GGAAGACGGA	GAAGGIGGAT	GACA 2450
	2460	2470	2480	2490	2500	2510	2520
بليبيد	لسياس	ليبيليين	بلينيابين	بليبيلين	<u>ىلىنىدلىن.</u>	بلينتانين	<u> </u>
GTTTCTGTAGCAGTCAACCCAGACCGAGTAACCAGGAGAAATGCTCAGGAGAGTGCAGCACAGGTGGATG 2520							
GCGCTATTCAGCCTGGACCGAATGTTCTAGAAGCTGTGATGGTGCTACCCAGAGAAGAAGAAGAGCAATTTGT 2590							
			ATGACAGCAA				

Fig. 9A

10	20	30	40	50	60	70
TCACGCACGCCTTCC						
CCCCGIGGACCACAA						· •
GGGCCACAGCCGAGI						
CCCACCICCCGICTA						
66666666666666						
360	370	380	390	400	410	420
					-	
CAGCACCIGIGGAGG						
GCIGGGCCCAAGGGI						,
GTCACCCCCACCTGC						
GCGGACCTTGAAGCC						
CGATCCGTCACCCGA						
710	720	730	740	750	760	770
GCCCCCGGATGTCC						
TCTGGGAAGCACCGT						
ATCACCCACCATGCC						-
GCCATGGCAATGCCA						
CATCTCCATCTACAA						
1060	1070	1080	1090	1100	1110	1120
لسلسلسل						
AGAGAAGCTGCAGCG						
CATTCGGCATGAACC						
GCTGCCCACATTAC						
TTTCTAGACTCGGGC	CIGGGGCICI	CCTGAACAAC	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	GACAGGACTI	TGTGTACCCC	ACAG 1330
TGGCACCGGGCCAAG	CCTACGATGC	AGATGAGCAA1	GCCGCTTTCA	CATGGAGTC	AAATCGCGTC	AGTG 1400
1410	1420	1430	1440	1450	1460	1470
ليبيطينيطينيي	<u> </u>	بليينانين	بليستليب	بليستليين	بالتستاليين	
TAAATACGGGGAGGI	CTCCACCGAC	CIGIOGIGICI	GAGCAAGAGC	CAACCOGTGCA	TCACCAACAC	CATC 1470
CCGGCCGAGGGC	'ACGCTGTGCC	AGACGCACACC	ATOGACAAGO	OGTGGTGCTA	CAAACGGGTC	TGTG 1540
TCCCCTTTGGGTCGC	GCCCAGAGGG	TGTGGACGGAC	CCIGGGGGC	CICCACICCA	TGGGGGGACT	GCAG 1610
CCGGACCTGTGGCGC	ccccicicc	ICTICTAGICG	TCACTGCGAC	CAGCCCCAGGC	CAACCATCGC	1680 ggc
AAGTACTGTCTGGGT	GAGAGAAGGCY	GCACCCCTCC	TGCAACACGC	ATGACTGTCC	.ccc1ccc1cc	CAGG 1750

Fig. 9A (con't)

1760	1770	1780	1790	1800	1810	1820
ليبيلينيانين	للسلسا	لبييلين	لسبلسب	لسلسي	بليسانيسب	ш
ACTICAGAGAAGIGC	AGIGITCIGA!	ATTTGACAGC	ATCCCTTTCC	GIGGGAAATI	CTACAAGTGGA	AAAAC 1820
GTACCGGGGAGGGG	OGIGAAGGCC:	IGCICGCICA	CGAGCCTAGC	GGAAGGCTTC	AACITCIACA(CGGAG 1890
AGGGCGCAGCCGTG	JIGGACGGGA(CACCCTGCCG	TCCAGACACG	GIGGACATII	GCGICAGIGGC	GAAT 1960
GCAAGCACGIGGGCI	GCGACCGAGI	CIGGGCICO	GACCIGCGGG	AGGACAAGIG	CCGAGIGIGIC	3GCGG 2030
TGACGGCAGTGCCTG	CGAGACCATC	GAGGGGGTCT	TCAGCCCAGC	CTCACCTGGG	GCCGGGTACG?	AGGAT 2100
2110	2120	2130	2140	2150	2160	2170
السياسياسيا						
GTCGTCTGGATTCCC						
CCCTGAAGGGAGACC	AGGAGICCCIV	CTCCTCGAG	GGGCTGCCTG	GGACCCCCCA	GCCCCACCGIV	TIGCC 2240
TCTAGCTGGGACCAC	CTTTCAACTG	CGACAGGGGC	CAGACCAGGI	CCAGAGCCTO	GAAGCCCTGGC	EACCG 2310
ATTAATGCATCTCTC						
CCCCCATCGCCCGTG	ACTOGCTGCO	CCCCTACTCC	TGGCACTATG	CGCCCTGGAC	CAAGIGCICG	3CCCA 2450
2460	2470	2480	2490	2500	2510	2520
<u> </u>	لتتبليين	لتتبليين	لتتسليين	لسيلس	لسلسل	
GIGIGCAGGCGTAG	CCAGGIGCAG	GCGGTGGAGT	GCCGCAACCA	GCTGGACAGC	TCCGCGGTCGC	cccc 2520
CACTACTGCAGTGCC	CACAGCAAGC	TGCCCAAAAG	GCAGCGCGCC	TGCAACACGG	AGCCITGCCC	ICCAG 2590
ACTGGGTTGTAGGGA	ACTGGTCGCT	CTGCAGCCGC	ACCICCGAIC	CAGGCGTGCG	CAGICGCICG	GICGI 2660
GTGCCAGCGCCGCGT	CICIGCCGCG	GAGGAGAAGG	CGCTGGACGA	CAGCGCATGC	CCGCAGCCGC	GCCCA 2730
CCTGTACTGGAGGCC	TGCCACGGCC	CCACTIGCCC	TCCGGAGTGG	ECAACCCTCC	ACTGGTCTGAG	GIGIA 2800
2810	2820	2830	2840	2850	2860	2870
ليبيبليييا						
CCCCAAGCTGTGGGC	CIGGICICCG	CCACCGAGIC	GICCITIGIA	AGAGTGCAGA	TCAACGATĆT	ACICI 2870
GCCCCTGGGCACTG	CCTTCCTGCA	GCCAAGCCAC	CATCTACTAT	CCGATGTAAC	TICCCCCCC	GCCCT 2940
CCIGCCCGCIGGGIG	ACCAGIGAGI	GCCGTGAGTC	TICCACACAC	FIGIGGCCICC	XGCCAGCAGCA(GCGCA 3010
CAGTGCGCTGCACCA						
GCAGCAGIGIGAGGC	CAAGIGIGAC	AGIGIGGIGC	CGCCIGGAG!	ATGCCCAGAA	GAATGCAAGG	ATGTG 3150
3160	3170	3180	3190	3200	3210	3220
ليبيلينيليين	لتتطييب	ليتبيليين	ليتتليين	لىسلىسا	لسيلسي	
AACAAGGIGGCTTAC	TGCCCCCTGC	TGCTCAAATT	TCAGTTCTG	[AGCCGAGCC]	CACTTCCGCCA	GATGT 3220
GCTGCAAAACCTGCC	CAAGGCCGCta	gggtacctgg	jaaccaacct <u>c</u>	ggagcacaggc	tgaggcaggg	gacat 3290
cccactggagaggg	atgagggaaa	.ggggggcttg	gaattgaaggg	gtgagatgcag	gttgaaagtta	tttat 3360
tgggtaaccctacag	ggctcctgac	taaggggtgg	gagaagagctg	getacccage	gaccctctgc	tgtat 3430
cttgcccagttgata	igtgaagagag	gaggactcctt	gttgcacaca	atatttaagto	cctagcaccc	etccc 3500

Fig. 9A (con't)

				\			
	3510	3520	3530	3540	3550	3560	3570
لمسلا	mulmi	ليسلسب	لتنتانين	سياسي	ليبيلين	ليبيلينيا	البييا
accct	ttgatcggaa	tatgtactg t	.gaagagtggg	ggtggggagg	ggtgtgctgc	tgeeetgeee	ecetge 3570
							caccac 3640
	tgtagccctc						
							actcct 3780
caccaagaagccttacattaaaaaagttgtgttatcctacaaaaaaaa							
	3860	3870	3880	3890	3900	3910	3920
<u> </u>							
ggtacccaattcgcgctatagtagatngggtntta 3885							

26/54 Fig. 9B

human ADAM TS-8/10
10 20 30 40 4 /
SRTPSGLKMSSCPVWRAMRSPSPPAWITTGHCWPSRHLLP 40
GAAPRHOGHSRVPPLLQSGLASTHFLLNLTRSSRLLAGRV 80
sveywtreglawqraarphclyaghlqgqassshvalstc 120 gglhglivadeeeylieplhggpkgsrspeesgphvvykr 160
SSLRHPHLDTACGVRDEKPWKGRPWWLRTLKPPPARPLGN 200
210 220 230 240 Make prolease
ETERCOPCILKREVSRERYVETLVVADKMMVAYHCRRDVEQ 240
YVLAIMNIVAKLFQDSSLGSTVNILVIRLILLITEDQPTLE 280 SVSRERY
ITHHAGKSLDSFCKWQKSIVNHSGHCNAIPENGVANHDTA 320
VLITRYDICIYKNKPCGILGLARWAECVSAREAAASMRTL 360
AATSVHICHEIGHIFGMNHDGVGNSCGARGQDPAKLMAAH 400
410 420 430 440
ITMKTNPFVWSSCNRDYITSFLDSGLGLCLNNRPPRQDFV 440
YPTVAPGQAYDADEQCRFQHGVKSRQCKYGEVCSELWCLS 480
KSNRCITNSIPAAEGILCQIHTIDKGWCYKRVCVPFGSRP 520
EGVDGAWGPWTPWGDCSRTCGGGVSSSSRHCDSPRPTIGG 560
KYCLGERRRHRSCNIDDCPPGSQDFREVQCSEFDSIPFRG 600
610 620 630 640
KFYKWKTYRGGGVKACSLTSLAEGFNFYTERAAAVVDGTP 640
CRPDIVDICVSGECKHVCCDRVLGSDLREDKCRVCGGDGS 680
ACETIEGVFSPASPCAGYEDVVWIPKGSVHIFIQDLNLSL 720
SHLALKGDQESLLLEGLPGTPQPHRLPLAGTTFQLRQGPD 760
QVQSLFALGPINASLIVMVLARTELPALRYRFNAPIARDS 800
810 820 830 840
THE TARK THE TARK OF THE TARK
LPPYSWHYAFWTKCSAQCAGGSQVQAVECRNQLDSSAVAP 840
HYCSAHSKLPKRQRACNTEPCPPDWVVGWSLCSRSCDAG 880 VRSRSVVCQRRVSAAEEKALDDSACPQPRPPVLEACHGPT 920
CPPEWATLDWSECTPSCGPGLRHRWLCKSADQRSTLPPG 960
HCLPAAKPPSIMRCNLRRCPPARWVISEWGECSTQCGLGQ 1000
INTEREST POSTURATED OF TURBUS TOPINO CONTRACTOR TOPINO

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Fig. 9B (con't)

1010 1020 1030 1040

QQRTVRCTSHTGQPSRECTEALRPSTMQQCFAKCDSVVPP 1040

GDGPEECKDVNKVAYCPLVLKFQFCSRAYFRQMCCKTCQG 1080

R 1081

Fig. 10A

partial requerce of mouse ADAM 75-10								
partial requerce of mouse ADAM 75-10 10 20 30 40 (See figure)								
AGCAGCAGCTGTGGTGGATGGAACACCCTGCCGCCCTGAC 40								
ACGGTGGACATTTGTGTCAGCGGCGAGTGCAAGCATGTAG 80								
GCTGTGACAGGTCCTGGGTTCTGATCTCCGAGAGGACAA 120								
ATGCCGTGTGTGGGGGTGATGCCAGTGCCTGTGAGACC 160								
ATTGAAGGIGICITTAGCCCAGCITTGCCAGGAACTGGGI 200								
210 220 230 240								
ATGAGGACGTCGGATCCCCAAAGGCTCGGTCCACAT 240								
TITCATCCAAGATCTGAACCTGTCCCTGAGTCACCTGGCC 280								
CTAAAGGGGACCAAGAGTCTCTGCTACTGGAGGGGCTAC 320								
CTGGGACCCCCAACCTNACCGCCTTCCCCTGGNTGGGAC 360								
CACATTICATCTACGGCAGGGCCGGACCAGGCACAGAGC 400								
410 420 430 440								
CIGGAAGCCCIGGGACCCATTAATGCATCICTCATCATCA 440								
TGGTGCTGGCCCAGGCAGGTTGCCTGCTCTCCACTACCG 480								
CITCAATGCACCCATTGCCCGGGATGCACTGCCTCCCTAC 520								
TCCTGGCACTATGCCCCCTGGACCAAATGCTCAGCCCAGT 560								
GIGCAGGCGGCAGGICCAAGIAGIGGAGIGCCGAAA 600								
610 620 630 640								
TCAGCTGGACAGCTCAGCAGTGGCCCCACACTACTGTAGT 640								
GGCCACAGTAAATTGCCCAAGAGGCAGCGTGCCTGCAACA 680								
CAGAACCATGTCCACCAGATTGGGTTGTAGGAAACTGGTC 720								
ACCCTGCAGCCGTAGCTGTGTGTGTGCGTAGCCGC 760								
TCAGIGGIGICCCAACGCCGGIGICIGCIGCAGAGGAAA 800								
810 820 830 840								
AAGCCTTAGACGACAGTGCCTGTCCACAGCCACGCCCCACC 840								
TGTCCTGCAGGCCTGCCAATGTGCCCTCCTGAG 880								
TGGCCAACCCTCGACTGTGTACCCCCAAGCTGTG 920								
GCCTGGTCTCCGCCACCGAGTGGTCCTTTGTAAGAGTGC 960								
AGATCAACGATCTACTCTGCCCCCTGGGCACTGCCTTCCT 1000								

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Fig. 10A (con't)

1010 1020 1030	1040
	<u></u>
GCAGCCAAGCCACCATCTACTATGCGATGTAACTTGCG	GCC 1040
GCTGCCCTCCTGCCCGCTGGGTGACCAGTGAGTGGGGT	IGA 1080
GIGITCCACACAGIGIGGCCTCGGCCAGCAGCAGCCA	ACA 1120
GIGCGCIGCACCAGCCACCCACCCATCTCGAGA	AGT 1160
GCACTGAAGCCITGCGGCCATCCACCATGCAGCAGTGT	IGA 1200
1210 1220 1230	1240
maliinlanduuluuluuluulu	<u></u>
GCCCAAGTGTGACAGTGTGGTGCCCCCTGGAGATGCCC	CCA 1240
GAAGAATGCAAGGATGTGAACAAGGTGGCTTACTGCCC	CCC 1280
TGGIGCTCAAATTTCAGTTCTGTAGCCGAGCCTACTTC	CCG 1320
CCAGATGTGCTGCAAAACCTGCCAAGGCCGCTAGGGTA	ACC 1360
TGGAACCAACCTGGAGCACACGCTGAGGCAGGGGACAT	rcc 1400
1410 1420 1430	1440
	ш
CACTGGAGAGGCATGAGGGAAAGGGGGCTTGAATTG	GAA 1440
GGGTGAGATGCAAGTTGAAAGTATTTATTTGGGTAACC	CCC 1480
TACAGGGCTTCTGACTTAAGGGGTGGAGAANAGCTGGC	CTA 1520
CCCCAGGGACCCTTTTGTTGGATCTTGGCCCANITGAT	
TGAAGAGAGACTTCTTGGTGVACACATTTTTAAGT	rcc 1600
1610 1620 1630	1640
	ш
TTAGACCCTTCCACCIVITGATCGGATATGTCTGGGAAG	GAG 1640
QN 1642	• •

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Fig. 10B

	10	20	30	4 0	monse	ADAM TSIO	
سيلينين	سلسست	بالبستانية	بلبيياب				
AAAVVDGI	PCRPDIVDI	CVSGECKHV	CORVLGSDLF	EDK 4	Ю		
CRVCGGDG	SACETIEGV	FSPALPGIG	YEDVVWIPKGS	3 IHV	10		
FIQDLNLS	LSHLALKGI	QESLLLEGL	PGTPQPXRLPI	XGT 1	.20		
TFHLRQGF	DQAQSLEAI	GPINASLIII	<i>I</i> VLAQAELPAI	HYR 1	-60		
FNAPIARE	ALPPYSWHY	'APWIKCSAQ	CAGGSQVQVVE	CRN 2	200		
	210	220	230	240			
سلسب	بيلينييل	علىبىلىب	بلينيلين	حلب			
QLDSSAVA	PHYCSCHSK	LPKRQRACIV	repcppdwvc	anns 2	240		
RCSRSCDA	GVRSRSVVC	QRRVSAAEE	KALDDSACPQE	RPP 2	280	•	
			GPGLRHRVVLC				₽
			RCPPARWVTSE				
CSTQCGLG	QQQRTVRC1	SHIGQPSRE	TEALRPSIM	XXCE 4	100	•	
	410	420	430	440			
سلسب	سلسسلب	بلينيلين	بالسالية	سلب			 .
AKCDSVVE	PGDGPEEC	OVNKVAYCP.	LVLKFQFCSRA	YFR 4	140		
QMCCKTCC	GR 450						

Fig. 11A

Ligated 459225+482392 with Sac I(168)&Eco RI(or Not I) Cloning site:5';Eco RI 3';Not I Vector; PI7T3 pac.

You can put this construct to pcDNA3.1(+) for transfection 5'-UTR is 50bp &3'-UTR is 175bp

210-215; in 482392 it's TCCTAC(SY).

	10	20	30	40		
سلسب	سلسسلب	لتستليد	لتستليب	ــــــــــــــــــــــــــــــــــــــ		
gaattcg	gcacgaggca	gtgtccga	ttctgattco	oggcaa 40		
ggatcca	agcATGGAAT	GCTGCCGT	CGGGCAACTC	CCIGGC 80		
ACACTGC:	ICCICITICI	GCTTTCC	TGCTCCTGAC	FITCCA 120		
GGACCGC	ACgctCCGAG	GAGGACCG	GGACGGCCII	ATGGGA 160		
TGCCTGG	GCCCATCGA	GTGAATGC	TCACGCACCI	rgcggg 200		
	210	220	230	240		
سلسب	بيلينيلي	لبينانيا	لتتبليين	<u> </u>		
GCIGGGG	CCCCAACTC	TCTGAGGO	GCTGCCTGAC	CAGCA 240		
AGAGCIG.	IGAAGGAAGA	AATATCCG	ATACAGAACA	ATGCAG 280		
TAATGIG	GACIGCCCAC	CAGAAGCA	GGTGATTTCC	GAGCT 320		
CAGCAAT	GCTCAGCTCA	TAATGATG	TCAAGCACCA	ATGGCC 360		i
AGITITA	IGAAIGGCTI	CCIGIGIC	TAATGACCCI	GACAA 400		
	410	420	430	440		
سلسب	سلسسلب	لتستليد	لتتبليين	ــــــــــــــــــــــــــــــــــــــ		
CCCATGIT	ICACICAAGI	GCCAAGCC	AAAGGAACAA	ACCCTG 440		
	. 					
GIIGIIG	AACTAGCACC	TAAGGICT	TAGATOGTAC	CCCTT 480		:
	ACTACCACC AGAATCTTTG			- -		:
GCTATACA		GATATGTO	CATCAGIGGI	TTATG 520		:
GCTATACA CCAAATTO	AGAATCTTTG	GATATGTG ATCACCAG	CATCAGIGGI CIGGGAAGCA	TTATG 520 ACCGTC 560		
GCTATACA CCAAATTO	AGAATCTTTG STTGGCTGCG	GATATGTG ATCACCAG	CATCAGIGGI CIGGGAAGCA	TTATG 520 ACCGTC 560		; •
GCTATACA CCAAATTO	AGAATCTTTG FTTGGCTGCG ATAACTGTGG	GATATGTG ATCACCAG GGICTGCA	CATCAGIGGI CTGGGAAGCA ACGGAGATGG	TTATG 520 ACCGTC 560 ACCGTCA 600		•
GCTATACZ CCAAATTO AAGGAAGZ	AGAATCTTTG FTTGGCTGCG ATAACTGTGG	GATATGIO ATCACCAG GGICIGCA 620	CATCAGIGGI CTGGGAAGCA ACGGAGATGG 630	TTATG 520 ACCGTC 560 ACCGTCA 600 640		
GCTATACZ CCAAATTO AAGGAAGZ CCTGCCGC CGCAACCZ	AGAATCTTTG STTGGCTGCG ATAACTGTGG 610	GATATGIO ATCACCAG GGICIGCA 620 LLLLLLLL GGGCAGTA ATACTGIO	CATCAGIGGI CIGGGAAGCA ACOGAGATOG 630 LLLLLL IAAATCCCAG GITGCAATTC	TTATG 520 ACCGIC 560 AGICCA 600 640 ACTICIC 640 ACCITAT 680	·	·
GCTATACZ CCAAATTO AAGGAAGZ CCTGCCGC CGCAACCZ GGAAGTAC	AGAATCTTTG STTGGCTGCG ATAACTGTGG 610 CTGGTCCGA AATCGGATG	GATATGIO ATCACCAG GGICIGCA 620 LLLLLLL GGGCAGTA ATACTGIG	CATCAGIGGI CTGGGAAGCA ACGGAGATGG 630 LLLLLLLL IAAATCCCAG GTTGCAATTC	TTATG 520 ACCGTC 560 EGICCA 600 640 ECICIC 640 ECICIC 640 ECICAT 680 ETGATC 720		·
GCTATACA CCAAATTC AAGGAAGA CCTGCCGC CGCAACCA GGAAGTAC ACTTATATA	AGAATCTTTG ETTGCTGCG ATAACTGTGG 610	GATATGTO ATCACCAG GGTCTGCA 620 LLLLLLLL GGGCAGTA ATACTGTG CCTTGTCT AAAACCCT	CATCAGTEGT CTGGGAAGCA ACGGAGATEG 630 LLLLLLLL TAAATCCCAG GTTGCAATTC TAAAAGGTCC CCAGGGGACT	ACCGTC 560 ACCGTC 560 ACCGTC 640 ACTCTC 640 ACCTAT 680 ACCTAT 680 ACCTAT 720 AAAAGG 760		·
GCTATACA CCAAATTC AAGGAAGA CCTGCCGC CGCAACCA GGAAGTAC	AGAATCTTTG STTGGCTGCG ATAACTGTGG 610 CTGGTCCGA AATCGGATG	GATATGTO ATCACCAG GGTCTGCA 620 LLLLLLLL GGGCAGTA ATACTGTG CCTTGTCT AAAACCCT	CATCAGTEGT CTGGGAAGCA ACGGAGATEG 630 LLLLLLLL TAAATCCCAG GTTGCAATTC TAAAAGGTCC CCAGGGGACT	ACCGTC 560 ACCGTC 560 ACCGTC 640 ACTCTC 640 ACCTAT 680 ACCTAT 680 ACCTAT 720 AAAAGG 760		•

The second section of

32/54 Fig. 11A (con't)

810 820 830 840	
AATTCTAGTGTGGACTTCCAGAAATTTCCAGACAAAGAGA 840	
TACTGAGAATGGCTGGACCACTCACAGCAGATTTCATTGT 880	•
CAAGATTCGTAACICGGGCTCCGCTGACAGTACAGTCCAG 920	
TICATCITCTATCAACCCATCATCCACCGATGGACGGAGA 960	
CGGATTTCTTCCTTGCTCAGCAACCTGTGGAGGAGGTTA 1000	
1010 1020 1030 1040	
<u> </u>	
TCAGCTGACATCGGCTGAGTGCTACGATCTGAGGAGCAAC 1040	
CGTGTCGTTCCTGACCAATACTGTCACTATTACCCAGAGA 1080	
ACATCAAACCCAAACCTTCAGGAGTGCAACTTGGA 1120	
TCCTTGTCCAGCCAGTGACGGATACAAGCAGATCATGCCT 1160	
TATGACCICTACCATCCCCTTCCTCGGIGGGAGGCCACCC 1200	
1210 1220 1230 1240	
<u> </u>	
CATGGACCGCGTGCTCCTCGTGTGGGGGGGGCATCCA 1240	
GAGCCGGCAGTTTCCTGTGTGGAGGAGGACATCCAGGGG 1280	
CATGICACTICAGIGGAAGAGIGGAAATGCATGTACACCC 1320	
CTAAGATGCCCATCGCGCAGCCCTGCAACATTTTTGACTG 1360	
CCCTAAATGGCTGGCACAGGAGTGGTCTCCGTGCACAGTG 1400	
1410 1420 1430 1440	
ACGIGIGGCCAGGCCICAGATACCGIGIGGICCICIGCA 1440	
TCGACCATCGACGACACACACGACGCTGTAGCCCAAA 1480	
AACAAAGCCCCACATAAAAGAGGAATGCATCGTACCCACT 1520	
CCCTGCTATAAACCCAAAGAAACTTCCAGTCGAGGCCA 1560	
AGTTGCCATGGTTCAAACAAGCTCAAGAGCTAGAAGAAGG 1600	
1610 1620 1630 1640	
ACCTCCTGTCACACGACCCCTCGTAAgttgtaaaagca 1640	
cagactgttctatatttgaaacttttgtttaaagaaagca 1680	
gtgtctcactggttgtagctttcatgggttctgaactaag 1720	
tgtaatcatctcaccaaagctttttggctctcaaattaaa 1760	
gattgattagtttcaaaaaaaaaaaaaaaaaagatgcggc 1800	

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33/54 g. 11A (con't)

1810 1820 1830 1840

ogc 1803

•••

34/54 Fig. 11B

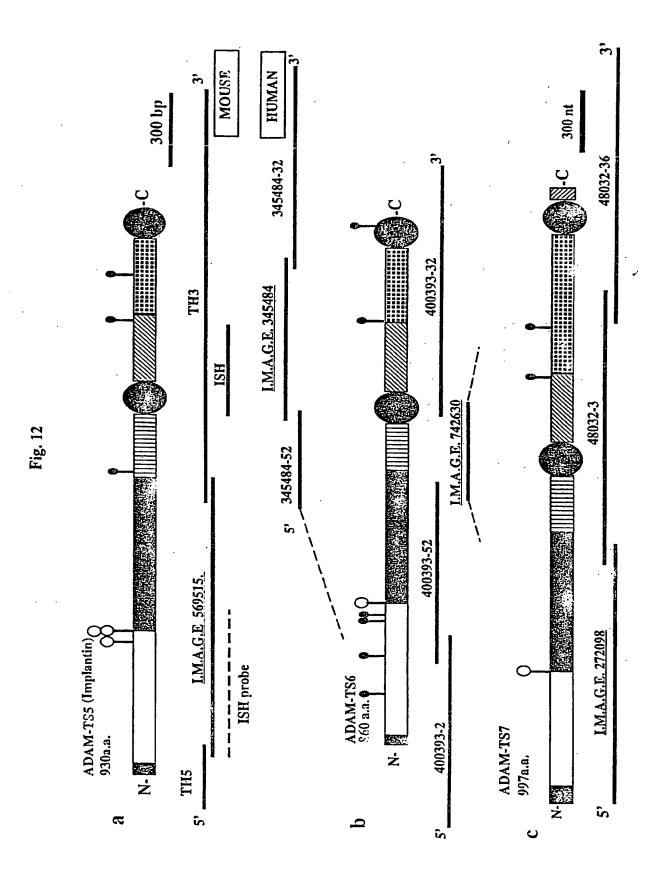
	Asp(D)	30	# cua	Leu(L)	3	# uca	Ser(S)		_	Val(V)	6
ugc	Cys (C)	26	# cuc	Leu(L)	11	# ucc	Ser(S)	10	#	Val(V)	29
ugu	Cys(C)	10	# cug	Leu(L)	14	# ucg	Ser(S)	5	# nnn	??? (X)	0
	Cys(C)	36	# cuu	Leu(L)	6	# ucu	Ser(S)	5	# TOTA	L	526
caa	Gln(Q)	7	# uua	Leu(L)	4	#	Ser(S)	43	# .		
	· -										

Created: Wednesday, May 5, 1999 10:19 AM

Ligated 459225+482392 with Sac I(168)&Eco RI(or Not I) Cloning site:5';Eco RI 3';Not I Vector; PI7T3 pac.

human ADAM-TSRI Adam-75 related protein-1.

10 20 30 40	
MECCRRATEGILLELAFILLSSRTARSEEDRDGLWDAWG 40	Signal pephole
PWSECSRTCGCGAANSLRRCLSSKSCEGRNIRYRTCSNVD 80	1,700
CPPEAGDFRAQQCSAHNDVKHHGQFYEWLPVSNDPDNPCS 120	
LKCQAKGITLVVELAPKVLDGTRCYTESLDMCISGLCQIV 160	
GCDHQLGSTVKEDNCGVCNGDGSTCRLVRGQYKSQLSATK 200	
210 220 230 240	
SDDIVVAIPYGSRHIRLVLKGPDHLYLEIKTLQGIKGENS 240	
LSSIGTFLVDNSSVDFQKFPDKEILRMAGPLTADFIVKIR 280	
NSGSADSTVQFIFYQPIIHRWREIDFFPCSATCGGGYQLT 320	
SAECYDLRSNRVVADQYCHYYPENIKPKPKLQECNLDPCP 360	(C) YYPENIKPKFKLQE
ASDGYKQIMPYDLYHPLPRWEATPWIACSSSCGGGIQSRA 400	_
410 420 430 440	·
VSCVEEDIQGHVISVEEWKCMYTPKMPIAQPCNIFDCPKW 440	(C) QELEEGAAV
LAQEWSPCIVICGQGLRYRVVLCIDHRGMHICGCSPKIKP 480	and company from Al
HIKEECIVPTPCYKPKEKLPVEAKLPWFKQAQELEEGAAV 520	C- term not epitope for AL
SEEPS. 526	4 1 laces the
SEEPS. 526 Similar to ADAM-TS farm	ly one
31000lax 10	parin domain. Om
monetalloprolease and assure	inwhiler of the
humberie is that this may	re a
prometalloprolease and disinter hypothesis is that this may	
formily	
V	



d .	
* MRLEWASILILILILSASCISIAADSPAAAPAQDKTRQPQAAAAAAEPDQPQGEETRERGHLQPLAGQRRSGGLVHNIDQ	80
LYSGGGKVGYLVYAGGRRFLLDLERDDIVGAAGSIVIAGGGLSASSGHRGHCFYRGIVDGSPRSLAVFDLCGGLDGFFAV	160
KHARYTLKPLLRGSWAEYERIYGDGSSRILHVYNREGFSFEALPPRASCETPASPSGPQESPSVHSRSRRRSALAPOLLD	040
	240
• •	
HSAFSPSCNAGPQTWWRRRRRSISRARQVELLLVADSSMARMYGRGLQHYLLJTLASIANRLYSHASTENHTRLAVVKVVV	320
* * * * *	
LIDKDISLEVSKNAATILKNFCKWQHQHNQLGDDHEEHYDAAILFIREDLCGHHSCDILCMADVGIICSPERSCAVIEDD	400
GLHAAFTVÆHEIGHLIGLSHIDEKFÖEENFGTTEDKRIMESILTSIDASKEWSKÖTSATITEFLIDGHGVÖLLDLERKQI	480
GHLIGLSHDDSKFCEETFGSTELKRIMSSILTSIDASKPWSKCTSATTTEFLDDGHGNCLLDLPRKQI	
<u></u> →Dis * * * * * * * *	
LGPEEL PGQTYDATQQCNLTFGPEYSVCPGMDVCARLWCAVVRQGQMVCLTKKLPAVEGTPCGKGRVCLQGKCVDKTKKK	560
LGPEELFGQTYDATQQCNLTFGPEYSVCPGXDVCARLWCAVVRQGQMVCLTKKLPAVEGTPCGKGRICLQGKCVDKTKKK	
YYSTSSHENWGSWGPWGQCSRSCOGGVQFAYRHCNNPAPRNSGRYCTGKRAIYRSCSVTPCPPNGKSFRHDQCEAKNGYQ	640
YYSTSSHCMMGSWGSWGOCSRSCGGGVOFAYRHONDAPRINGRYCTGKRAIYHSCSIMPCPPNGKSFRHDQCEAKNGYQ	010
* * * * *	
SDAKGVKTFVEWVPKYAGVLPADVCKLICRAKGTGYYVVFSPKVTDGTECRPYSNSVCVRGRCVRTGCDGIIGSKLQYDK	7 20
SDAKGVKTFVEMVPKYAGVLPADVCKLITCRAKGIGYYVVFSPKVTDGTECRPYSNSVCVRGKCVRTGCDGLIGSKLQYDK	
* ** Spacer domain CGVCGCDNSSCTKIIGTFNKKSKGYTDVVRIPEGATHIKVRQFKAKDQTRFPAYLALKKKTGEYLINGKYMISTSETTID	800
CGVCGCINSSCIKIUGIFNKKSKGYIDVVRIPEGATHIKVRQFKAKDQIRFTAYLALKKKNGEYLINGKYMISTSETIID	800
INGTVMNYSGWSHRDDFLHGYGYSATKEILIVQILATDPIKALGVRYSFFVPKKTTQKVNSVISHGSNKVGPHSTQLQWV	880
$\textbf{INGIVMNYSGWSHRDDFLHGMGYSATKEILIVQILAIDPTKPLDVRYSFFVPKKSIPKVNSVTSHGSNKVGSHTSQPQ\underline{\textbf{MV}}$	
* * * * * * * * * * * * *	000
TGPWLACSRTCDTGWHTRTVQCQDGNRKLAKGCLLSQRPSAFKQCLLKKC TGPWLACSRTCDTGWHTRTVOCODGNRKLAKGCPLSQRPSAFKQCLLKKC	930
SOURCE AND	

Fig. 13

Hurskainen et al[^]. Fig. 2a

METIMKTLTWILSLIMASSEFHSDHRLSYSSQEEFLTYLEHYQLTTPIRVDQXGAFLSFTVKNEKHSRRRRSMDPIDPQQ 80

AVSKLFFKLSAYGKHFHLNLTTMTDFVSKHFTVEYWGKDGPQWKHDFLLNCHYTGYLQDQRSTTKVALSNCVGLHGVTAT 160

EDEEYFTEPLKNTTEDSKHFSYENGHPHVIYKKSALQQRHLYDHSHCGVSDFTRSGKPWMINDTSTVSYSLPINWTHIHH 240

RQKRSVSTERFVETLVVALKMMVGYHCRKDIEHYTLSVMNIVAKLYRDSSLGWVNITVARLIVLTTEDQPALEINHADK 320

SLDSFCKWQKSTLSHQSDGNTTPENGIAHHDNAVLITRYDICTYKNKPCGTLGLASVAGNCEPFRSCSINEDIGLGSAFT 400

LAHEIVHNFGMHDETGNSCCRKVMQQNYGSSHYCEYQSFFLVCLQSRLHHQLFREVCRELWCLSKSNRCVTNSTPAAE 480

GTLCQTGNIEKGWCYQCDCVPFGTWFQSIDGGWGPWSLWCECSRTCGGGVSSSLRHCDSPAPSGGGKYCLGERKRYRSCN 560

TDPCPLGSRDFREKQCADFDNMPFRGKYYNWKPYTGGGVKPCALWCLABGYNFYTERAPAVIDGTQCNADSLDICTNGEC 640

KHVGCINILGSDAREDRCRVCGGGGSTCDATEGFFNDSLFRGGYMEVVQIPRGSVHIEVREVAMSKNYTALKSBCDDYYT 720

NCAWTILWPRKFDVAGTAFHYKRPTDEPESLEALGPTSENLIVWILLQEQNLGTRYKFNVPITRTGSGDNEVGFTMHQP 800

WSECSATCAGGKMPTRQPTQRARWRIKHILLSYALCILLKKLIGNISCRFASSCNLAKETIL 860

MFGGPSPRSPAPILRPLLLLCALAPGAPGPAPGRATEGRAALDIVHPVRVDAGGSFLSYELWPRALRKRDVSVRRDAPA 80

FYELQYRGRELRFNLTANQHLLAPGFVSETRRRGGLGRAHIRAHTPACHILGEVQDPELEGGLAAISACDGLKGVFQLSN 160

EDYFIEPLDSAPARRCHAQPHWYKRQAPERLAQRGDSSAPSTCGVQVVPELESRRERWEDRQQWRRPRLRRLHQRSVSK 240

EKWWETLWADAKWEYHGQPQVESYVLTIMMWAGLFHDPSIGNPIHITTIVRIVLLEDEEEDLKITHHADWILKSFCKW 320

QKSINMKEDAHPLHHDTAILLITRKDLCAAMMRPCETLGLSHVAGMCQPHRSCSINEDIGLPLAFTVAHELGHSEGIQHIG 400

SCANDCEPVGKRPFIMPQLLYDAAPLIWSRCSRQYITRFLDRGWGLCLDDPPAKDIIDFPSVPPGVLYDVSHQCRLQYGA 480

YSAFCEDMINVCHILWCSVGTTCHSKLDAAVDGTRGGENKWCLSGECVPVGFRPEAVDGWSGWSAWSICSRSCGMGVOS 560

AERQCTOPTTPKYKGRYCVGERKRFRLCNLQACPAGRPSFRHVQCSHFDAMLYKGQLHTWPVWNDVNPCELHCRPANEYF 640

AKKLRDAVVDGTPCYQVRASRDLCINGICKNVGCDFEIDSGAMEDRGGVCHANGSTCHIVSGTFEEAEELGYVDVGLIPA 720

GAREIRIQEVAFAANFLALRSEDPEKYFLNGGWTQWNGDYQVAGTTFTYARRGWWENLTSPGPTKEFWWIQVPASRGPG 800

GCSRGGVPRPSTTHRSRRPGGVSPGSVTEPGSEPGPPAAASTSVSPSLKWPNLWAAVHROGWQAPLGLCGWRRHLVIMG 880

PRLPTQLLFQESNRGVHYEYTTHREAGGHDEVPPPVFSWHYGFWIKCTVTCCRGEKWRHSPTCRGLVSCQGHWLQLPAH 960

CWATTGLEVCFSEPQFSICEMRLAIALCPRPAGRUNG 997

Fig. 13 (con't)

		adamalysin II atrolysin A	HELGHNLGME HD HELGHNLGMV HD	
		hADAM-9 hADAM-10 hADAM-15 hADAM-17 mADAM-19	HELGHNLGMNHD HEVGHNFGSPHD HELGHSLGLDHD HELGHNFGAEHD HEIGHNFGMSHD	
	a	mADAM-TS1 hADAM-TS2 hADAM-TS3 hADAM-TS4 mADAM-TS5 hADAM-TS6 hADAM-TS7	HELGHVFNMP HD HETGHVLGME HD HETGHVLGME HD HELGHVFNML HD HELGHL LG LS HD HEIVHN FGMNHD HELGH S FG I Q HD	
	mADAM-TS1 hADAM-TS2 hADAM-TS3 hADAM-TS4 hADAM-TS5 hADAM-TS6 hADAM-TS7	W G P W G W G A W S W G A W S W G P W G W G P W S W S G W S	W G D C S R T C G G G V Q Y 20 F G S C S R T C G T G V K F 20 F G S C S R T C G G G V Q F 20 W G D C S R S C G G G V Q F 20 W G E C S R T C G G G V S S 20 W S I C S R S C G M G V Q S 20	0 0 0 0
b	mADAM-TS1 hADAM-TS2 hADAM-TS3 hADAM-TS4 hADAM-TS5 hADAM-TS6 hADAM-TS7	T M R E C R T R Q C R T R Q C S S R D C A Y R H C S L R H C A E R Q C		0 0 0 0
	mADAM-TS1 hADAM-TS2 hADAM-TS3 hADAM-TS4 hADAM-TS5 hADAM-TS6 hADAM-TS7	R V R Y R A Y D F Q A Y D F Q R T R F R R A I Y H R K R Y R R K R F R	C S R O D C 5 C N T E D C 5 C S L M P C 5 C N T D P C 5	2 2 2 2 2 2 2

Fig. 13 (con't)

Hurskainen et al^. Fig. 3

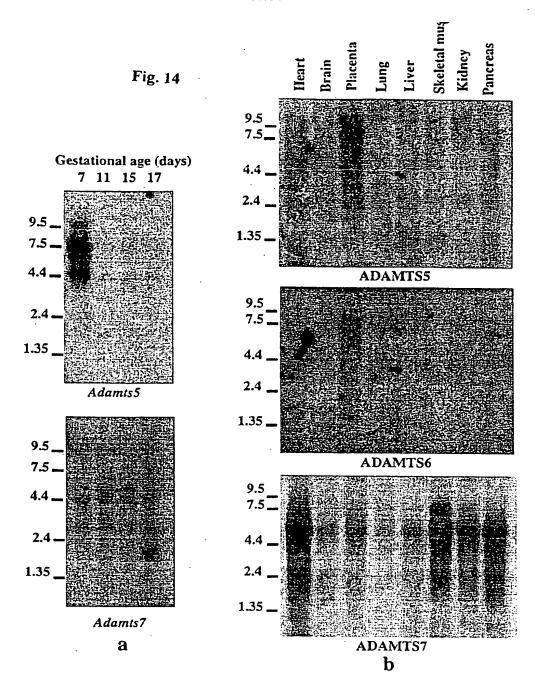
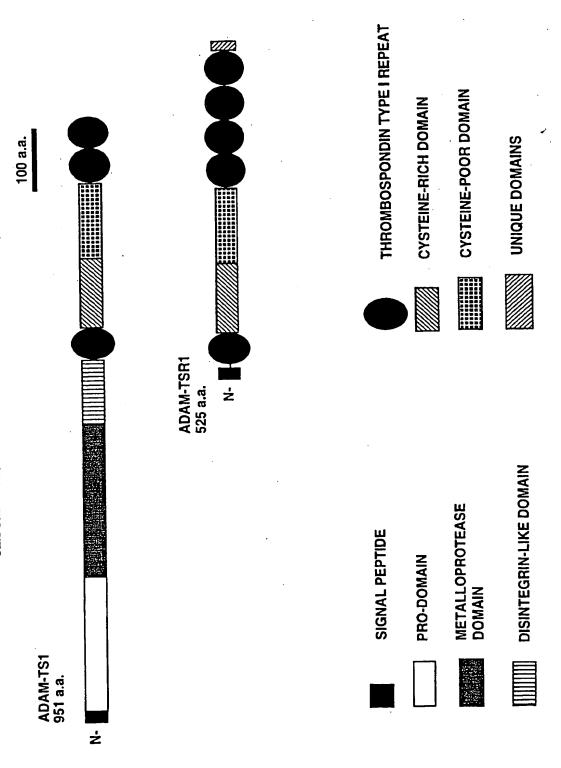


Fig. 15

ADAM-TS RELATED PROTEIN-1 (ADAM-TSR1)



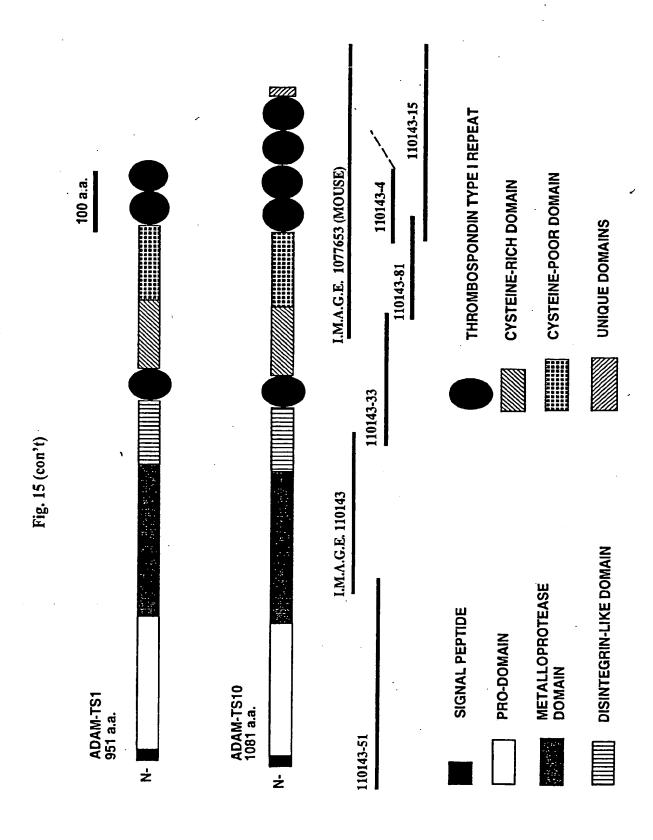


FIGURE 16 Pa

MSSCPWRAMRSPSPPAWITTCHCWPSRHLLP 40 GAAPRHGGHSRVPPLLOSGLASTHFLLNLTRSSRLLAGRV 80 SVEYWTREGLAWQRAARPHCLYAGHLQGQASSSHVAISTC 120 GGLHGLIVADEFEYLIEPLHGGPKGSRSPEESGPHVVYKR 160 SSLRHPHLDTACGVRDEKPWKGRPWWLRTLKPPPARPLGN 200 ETERGOPGLKRSVSRERYVETLVVADKMMVAYHGRRDVEQ 240 YVLAIMNIVAKLFODSSLGSTVNILVIRLILLIEDQPILE 280 ITHHAGKSLDSFCKWQKSIVNHSGHGNAIPENGVANHDTA 320 VLITRYDICIYKNKPCGTLGLARWAECVSAREAAASMRTL 360 AATSVHICHEIGHTFGMNHDGVGNSCGARGODPAKLMAAH 400 ITMKTNPFVWSSCNRDYITSFLDSGLGLCLNNRPPRQDFV 440 YPTVAPGOAYDADEOCRFOHGVKSROCKYGEVCSELWCLS 480 KSNRCITNSIPAAEGILCOIHIIDKGWCYKRVCVPFGSRP 520 EGVDGAWGPWIPWGDCSRTCGGGVSSSSRHCDSPRPTIGG 560 KYCLGERRRHRSCNIDDCPPGSQDFREVQCSEFDSIPFRG 600 KFYKWKTYRGGGVKACSLTSLAEGFNFYTERAAAVVDGTP 640 CRPDIVDICVSGECKHVGCDRVLGSDLREDKCRVCGGDGS 680 ACETIEGVFSPASPGAGYEDVVWIPKGSVHIFIQDLNLSL 720 SHLALKGDQESLLLEGLPGTPQPHRLPLAGTTFQLRQGPD 760 OVOSLEALGPINASLIVMVLARTELPALRYRFNAPIARDS 800 LPPYSWHYAPWIKCSAOCAGGSOVOAVECRNOLDSSAVAP 840 HYCSAHSKLPKRORACNTEPCPPDWVGNWSLCSRSCDAG 880 VRSRSVVCQRRVSAAEEKALDDSACPQPRPPVLEACHGPT 920 CPPEWAALDWSECTPSCGPGLRHRVVLCKSADHRATLPPA 960 HCSPAAKPPATMRCNLRRCPPARWAGEWGECSAQCGVGQ 1000 RORSVRCTSHIGOASHECTEALRPPITOOCEAKCDSPTPG 1040 DGPEECKDVNKVAYCPLVLKFOFCSRAYFROMCCKTCOGH 1080 Created: Thursday, October 01, 1998 11:05 PM

•	10	20	30	40	
بليبيد	سلسلس	سلسسلت	<u></u>	ш	
tcacgc	acgccttccgg	tctcaagATG	AGTICCIGIC	AG 40	
TCTGGA	GAGCTATGAGA	ICCCCTTCCCC	CACCCGCGTGC	AC 80	
CACAAO	GGGGCACTGCT	GCCTTCTCC	CACCICCIC	CC 120	
GGAGCA	GCGCCGCGCA	CGGGGGCCAC	AGCCGAGTCC	CC 160	
CICITO	TACAAAGIGGO	CTCGCCAGCA	CCACTICCIO	CT 200	

FIGURE						Pa		
						 .		
210	220	230	240)				
GAACCTGACCCGCAG			ACCIL.	240				
TCCGTGGAGTACTGG								
GGGGGGCCGGCCCC								
GGCCAGCCAGCAG								
GGAGGCCTGCACGGC	CIGATOGIGO	CAGACGAGGA	AGAGT	400				
4 10	420	430	440					
سيطسيطسي	لتتبيلينين	ليسلسب	للسب			- <u>-</u>		
ACCTGATTGAGCCCC	TGCACGGTGC	XGCCCAAGGGI	TCTCG	440			,	
GAGCCCGGAGGAAAG	TGGACCACAT	GIGGIGIACA	AGCGT	480			•	
TCCTCTCTGCGTCAC	CCCCACCTGC	ACACAGCCIC	TGGAG	520				
TGAGAGATGAGAAAC	CGIGGAAAGC	ECCGCCATGC	TGGCT	560				
GCGGACCTTGAAGCC	ACCGCCTGCC	AGACCCCTGC	XGGAAT	600				
610	620	630	640				•	٠
		لسلسلسا						
GAAACAGAGCGIGGC								
GCCGAGAGCGCTACC								
GATGATGGTGGCCTA								
TATGICCIGGCCATC		_	– -					
AGGACTCGAGTCTGG	GAAGCACCG1	TAACATCCTC	GIAAC	800				
810	820	830	840	•				
		ليبيليينا						
TCGCCTCATCCTGCT								
ATCACCCACCATGCC				-				
AGTGGCAGAAATCCA								
TGCCATTCCAGAGAA		•						
GTGCTCATCACACGC	TATGACATC	IGCATCTACAA	GAACA	1000				
1010	1020	1030	1040)				
						· · · · · · · · · · · · · · · · · · ·		
AACCCTGCGGCACAC								
TGTGAGCGCGAGAGA							•	
GCTGCCACAAGCGTT				,				
CATTCGGCATGAACC								
GGCCCGIGGICAGGA	CCCAGCCAAC	CICATGGCI	ECCCAC	1200	·			

FIGURE 16 (continued)
1210 1220 1230 1240
ATTACCATGAAGACCAACCCATTCGTGTGGTCATCCTGCA 1240
ACCGIGACTACATCACCAGCTTTCTAGACTCGGGCCTGGG 1280
GCTCTGCCTGAACAACCGGCCCCCAGACAGGACTTTGTG 1320
TACCCGACAGTGGCACCGGGCCAAGCCTACGATGCAGATG 1360
AGCAATGCCGCTTTCAGCATGGAGTCAAATCGCGTCAGTG 1400
1410 1420 1430 1440
<u> </u>
TAAATACGGGGAGGICIGCAGCGAGCIGIGGIGICIGAGC 1440
AAGAGCAACCGGTGCATCACCAACAGCATCCCGGCCGCCG 1480
AGGCACGCTGTGCCAGACGCACCATCGACAAGGGGTG 1520
GIGCTACAAACGGGICTGTGTCCCCTTTGGGTCGCGCCCA 1560
GAGGTGTGGACGGACCTGGGGCCGTGGACTCCATGGG 1600
1610 1620 1630 1640
GCGACTGCAGCCGGACCTGTGCCGGCGGCGTGTCCTCTTC 1640
TAGTCGTCACTGCGACAGCCCAGGCCAACCATCGGGGGC 1680
AAGTACTGTCTGGGTGAGAGAGGCGGCACCGCTCCTGCA 1720
ACACGGATGACTGTCCCCTGGCTCCCAGGACTTCAGAGA 1760
AGIGCAGIGITCIGAATTIGACAGCATCCCITTCCGIGGG 1800
1810 1820 1830 1840
AAATTCTACAAGTGGAAAACGTACCGGGGGGGGGGGGGG
AGGCCTGCTCGCGACGCCTAGCGGAAGGCTTCAACTT 1880
CTACACGGAGAGGGCGCAGCCGTGGTGGACGGGACACCC 1920
TGCCGTCCAGACACGGTGGACATTTGCGTCAGTGGCGAAT 1960
GCAAGCACGTGGGCTGCGACTCCTGGGCTCCGACCT 2000
2010 2020 2030 2040
GCGGGAGGACAAGIGCCGAGIGIGIGGCGGIGACGCCAGI 2040
GCCTGCGAGACCATCGAGGGCGTCTTCAGCCCAGCCTCAC 2080
CTGGGGCCGGGTACGAGGTCTGGATTCCCAAAGG 2120
CICCGICCACATCITCATCCAGGATCIGAACCICICICTC 2160

AGICACTIGGCCCIGAAGGGAGACCAGGAGTCCCTGCTGC 2200

FIGURE 16 (continued)

2210 2220 2230 2240
TO DO CO CONTROLOGICA CONTROLOG
TGGAGGGCTGCCTGGGACCCCCAGCCCCACCGTCTGCC 2240
TCTAGCTGGGACCACCTTTCAACTGCGACAGGGGCCAGAC 2280
CAGGTCCAGAGCCTCGAAGCCCTGGGACCGATTAATGCAT 2320
CTCTCATCGTCATGGTGCTGGCCCGGACCGAGCTGCCTGC
CCTCCGCTACCGCTTCAATGCCCCCATCGCCCGTGACTCG 2400
2410 2420 2430 2440
CIGCCCCCTACICCTGGCACTATGCGCCCTGGACCAAGT 2440
GCTCGGCCCAGTGTGCAGCCGGTAGCCAGGTGCAGGCGGT 2480
GGAGTGCCGCAACCAGCTGGACAGCTCCGCGGTCGCCCCC 2520
CACTACTGCAGTGCCCACAGCTGCCCAAAAGGCAGC 2560
GCGCCTGCAACACGGAGCCTTGCCCTCCAGACTGGGTTGT 2600
2610 2620 2630 2640
AGGGAACTGGTCGCTGCGAGCCGCAGCTGCGATGCAGGC 2640
GIGCGCAGICGCICGIGIGCCAGCGCCGCGICICIG 2680
CCGCGGAGGAGGCGCTGGACGACAGCGCATGCCCGCA 2720
GCCGCGCCACCIGIACTGGAGGCCTGCCACGGCCCCACT 2760
TGCCCTCCGGAGTGGGCCCTCGACTGGTCTGAGTGCA 2800
2810 2820 2830 2840
CCCCAGCIGCGGCCGCCACCGCGIGGICCT 2840
TTGCAAGAGCGCAGCCACGCTGCCCCCGGCG 2880
CACTGCTCACCCGCCCAAGCCACCGGCCACCATGCGCT 2920
GCAACTTGCGCCGCCCCCCGGCCCGCTGGGTGGCTGG 2960
CGAGTGGGTGAGTGCTCTGCACAGTGCGGCGTCGGGCAG 3000
3010 3020 3030 3040
CGCCAGCGCTCGGTGCCACCAGCCACACGGGCCAGG 3040
CGTCGCACGAGTGCACGGGCCCTGCGGCCCCACCAC 3080
GCAGCAGTGTGAGGCCAAGTGCGACAGCCCCAACCCCCGGG 3120
GACGGCCTGAAGAGTGCAAGGTGGAACAAGGTCGCCT 3160
ACIGCCCCIGGIGCICAAATTICAGITCIGCAGCCGAGC 3200

FIGURE 16 (continued)		F) E
3210 3220 3230	3240		_
CTACTTCCGCCAGATGTGCTGCAAAACCTGCCA	•		_
taggggggggggggacccggagccacagctgg	i		
tegecgceagectgcagegggccggccaaag		·	
cgggggggggaactgggagggaagggtgaga			
ggaagttatttattgggaacccctgcagggccc			
3410 3420 3430	3440		
	ــــــــــــــــــــــــــــــــــــــ		_
ggggataga 3409	•		

FIGURE 17

Molecular Weight 216301.30 Daltons

- 1934 Amino Acids
- 234 Strongly Basic(+) Amino Acids (K,R)
- 216 Strongly Acidic(-) Amino Acids (D,E)
- 477 Hydrophobic Amino Acids (A,I,L,F,W,V)
- 657 Polar Amino Acids (N,C,Q,S,T,Y)

7.734 Isolectric Point

24.102 Charge at PH 7.0

MQFVSWATLLTLLVRDLAFMGSPDAAAAVRKDRLHPRQVKLLETLSEYEIVSPIRVNALG	60
EPFPINVHFKRTRRSINSATDPWPAFASSSSSSTSPQAHYRLSAFGQQFLFNLTANAGFI	
A DE THE THE CONTROL BY COMMENT OF THE COMMENT OF T	
GGYFIEPLQSMDEQEDEEEQNKPHITYRRSAPQREPSTGRHACDTSEHKNRHSKDKKKTR	
ARKWGER INLAGDVAALNSGLATEAFSAYGNKTDNTREKRTHRRTKRFLSYPRFVEVLVV	
ADNRMVSYHGENLQHYILIILMSIVASIYKDPSIGNLINIVIVNLIVIHNEQDGPSISFNA	360
QTTLKNFCQWQHSNSPGGIHHDTAVLLTRQDICRAHDKCDTLGLAELGTTCDPYRSCSIS	
EDSGLSTAFTIAHELGHVFNMPHDDNNKCKEEGVKSPQHVMAPTLNFYTNPWMWSKCSRK	480
YITEFLDIGYGECLLNEPESRPYPLPVQLPGILYNVNKQCELIFGPGSQVCPYMMQCRRL	540
WCNNVNGVHKGCRTQHTPWADGTECEPGKHCKYGFCVPKEMDVPVTDGSWGSWSPFGTCS	
RTCGGGIKTAIRECNRPEPKNGGKYCVGRRMKFKSCNTEPCLKQKRDFRDEQCAHFDGKH	660
FNINGLLPNVRWVPKYSGILMKDRCKLFCRVACNTAYYQLRDRVIDGTPCGQDTNDICVQ	720
GLCRQAGCDHVLNSKARRDKCGVCGGDNSSCKTVAGTFNIVHYGYNIVVRIPAGATNIDV	
RQHSFSGETDDDNYLALSSSKGEFLLNGNFVVIMAKREIRIGNAVVEYSGSETAVERINS	840
TDRIEQELLLQVLSVGKLYNPDVRYSFNIPIEDKPQQFYWNSHGPWQACSKPCQGERKRK	900
LVCTRESDQLTVSDQRCDRLPQPGHITEPCGTGCDLRWHVASRSECSAQCGLGYRTLDTY	960
CAKYSRLDGKTEKVDDGFCSSHPKPSNREKCSGECNTGGWRYSAWTECSKSCDGGTQRRR	1020
AICVNTRNDVLDDSKCTHQEKVTTQRCSEFPCPQWKSGDWSECLVTCGKGHKHRQVWCQF	
GEDRLNDRMCDPETKPTSMQTCQQPECASWQAGPWVQCSVTCGQGYQLRAVKCIIGTYMS	
VVDDNDCNAATRPTDTQDCELPSCHPPPAAPETRRSTYSAPRTQWRFGSWIPCSATCGKG	
TRMRYVSCRDENGSVADESACATLPRPVAKEECSVTPCGQWKALDWSSCSVTCGQGRATR	
QVMCVNYSDHVIDRSECDQDYIPETDQDCSMSPCPQRTPDSGLAQHPFQNEDYRPRSASP	
SRTHVLGGNQWRTGFWGACSSTCAGGSQRRVVVCQDENGYTANDCVERIKPDEQRACESG	1380
PCPQWAYGWGECTKLCGGGIRTRLVVCQRSNGERFPDLSCETLDKPPDREQCNTHACPH	1440
DAAWSTGFWSSCSVSCGRGHKQRNVYCMAKDGSHLESDYCKHLAKPHGHRKCRGGRCPKW	1500
KAGAWSQCSVSCGRGVQQRHVGCQIGTHKLARETECNPYTRPESECECQGPRCPLYTWRA	1560
EEWQECTKTCGEGSRYRKVVCVDDNKNEVHGARCDVSKRPVDRESCSLQPCEYVWITGEW	1620
SECSVTCGKGYKQRLVSCSEIYIGKENYEYSYQITINCPGIQPPSVHPCYLRECPVSATW	
TH YOU. TO COME TO SEE THE TO SEE	1740
VKRLKGASEDGEYFLMIRCKLLKIFCACMHSDHPKEYVTLVHGDSENFSEVYGHRLHNPT	
ECPYNGSRRDDYYCRKDYTAACESSEOKTRTDI JISMOTTTITDI OEADTSECHIA DEADAG	1060

FIGURE 17 (cc inued)

Pa

DCYSAAKCPQGRFSINLYGTGLSLTESARWISQGNYAVSDIKKSPDGTRVVGKCGGYCGK 1920 CTPSSGTGLEVRVL 1934

10	20	30	40			
سيسلسسلس	لسيسلسم	سيطيب	لجسيا			
tgggggcagcggaggg	aggggtggg	raagcaccAT(CAGIT	40		
TGTATCCTGGGCCACA	CIGCTAACC	CICCIGGIG	CGGGAC	80		
CTGGCCGAGATGGGGA	GCCCAGACC	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	CCCTCC	120		
GCAAGGACAGGCTGCA	CCCGAGGCA	AGIGAAATT	ATTAGA	160		
GACCCTGAGCGAATAC	GAAATCGTC	TCTCCCATC	CAGIG	200		
210	220	230	240) '		
بالتنبالينيان	ليتبلين		لتتنيا		<u> </u>	· · · · · · · · · · · · · · · · · · ·
AACGCTCTCGGAGAAC	CCTTTCCCA	CGAACGTCC	ACTICA	240		*4
AAAGAACGCGACGGAG	CATTAACTC	TGCCACTGAC	CCCIG	280		
GCCTGCCTTCGCCTCC	TCCTCTTCC	TOCTOTACO	rcccc	320		
CAGGCGCATTACCGCC	TCTCTGCCT	TOGGCCAGC	AGITIC	360		•
TATTTAATCTCACCGC	CAATGCCGC	ATTTATCCC	ICCACT	400		
410	420	430	440)	•	
	لببيابي	سيلس	لسبل			
GITCACTGTCACCCTC	CTCGGGACC	CCCGGGGIG	AATCAG	440	•	
ACCAAGITITATICCG				480		
GITTCTACAAAGGCTA				520		
GCCGTCATCAGCCTC				560		
CGGTCTCATGATGGGG	GTTATTTY	ATTGAACCAC	TACAGT	600		
610	620	630	640)		
	<u></u>	سيلسب	لسبا			
CTATGGATGAACAAGA	AGATGAAG/	AGGAACAAAA	CAAACC	640		
CCACATCATTTATAGG	XCGCAGCGC(CCCCAGAGA	GAGCCC	680		
TCAACAGGAAGGCATG	CATGTGAC	ACCTCAGAAC	ACAAAA	720		
ATAGGCACAGTAAAGA	CAAGAAGA	AAACCAGAGC	AAGAAA	760		
ATGGGGAGAAAGGATT	'AACCTGGC.	rggigacgia	GCAGCA	800		
810	820	830	840)		
				-		
TTAAACAGCGGCTTAG	CAACAGAG	CATTITCIG	CTTATG	840	•	
GTAATAAGACGGACAA		_				
AAGGACAAAACGITITI						
GICITGGIGGIGGCAG						
GAGAAAACCTTCAACA	CTATATTT	CAACTTTAAT	GICAAT	1000)	

FIGURE 17 (col lued)

1010 1020 1030 104	
TGTAGCCTCTATCTATAAAGACCCAAGTATTGGAAATTTA	1040
ATTAATATTGTTATTGTGAACTTAATTGTGATTCATAATG	
AACAGGATGGGCCTTCCATATCTTTTAATGCTCAGACAAC	
ATTAAAAAACTTITGCCAGIGGCAGCATTCGAACAGTCCA	
GGIGGAATCCATCATGATACIGCIGITCTCTTAACAAGAC	
1210 1220 1230 124	
1210 1220 1230 124	±U
AGGATATCTGCAGAGCTCACGACAAATGTGATACCTTAGG	1240
CCTGGCTGAACTGGGAACCATTTGTGATCCCTATAGAAGC	-
TGITCTATTAGIGAAGATAGIGGATTGAGIACAGCTTTTA	
CGATCGCCCATGAGCTGGGCCCATGTGTTTAACATGCCTCA	
TGATGACAACAAATGTAAAGAAGAAGAGTTAAGAGT	
1410	
1410 1420 1430 144	TO.
CCCCAGCATGICATGGCTCCAACACTGAACTTCTACACCA	1440
ACCCTGGATGTGGTCAAAGTGTAGTCGAAAATATATCAC	
TGAGITTTTAGACACTGGTTATGGCGAGTGTTTGCTTAAC	
GAACCIGAATCCAGACCCIACCCITIGCCIGICCAACIGC	
CAGGCATCCTTTACAACGIGAATAAACAATGIGAATTGAT	
1610	
1610 1620 1630 164	
TTTTGGACCAGGTTCTCAGGTGTGCCCATATATGATGCAG	1640
TGCAGACGGCTCTGGTGCAATAACGTCAATGGAGTACACA	
AAGGCTGCCGGACTCAGCACACCCTGGGCCGATGGGAC	
GGAGIGCGAGCCIGGAAAGCACIGCAAGIATGGATTTTGT	
GTTCCCAAAGAAATGGATGTCCCCGTGACAGATGGATCCT	
1810 1820 1830 184	
GGGGAAGITGGAGTCCCTTTGGAACCTGCTCCAGAACATG	
TGGAGGGGCATCAAAACAGCCATTCGAGAGTGCAACAGA	_
CCAGAACCAAAAATGGTGGAAAATACTGTGTAGGACGTA	
GAATGAAATTTAAGICCTGCAACACGAGCCATGICTCAA	
GCAGAAGCGAGACTTCCGAGATGAACAGTGTGCTCACTTT	
	2000

₽s

50/54

FIGURE 17 (continued)

*	
2010 2020 2030 2040	
GACGGGAAGCATTTTAACATCAACGGTCTGCTTCCCAATG 2040	
TGCGCTGGGICCCTAAATACAGTGGAATTCTGATGAAGGA 2080	
CCGCTGCAAGTTGTTCTGCAGAGTGGCAGCGAACACAGCC 2120	
TACTATCAGCTTCGAGACAGTGATAGATCGAACTCCTT 2160	
GTGGCCAGGACACAAATGATATCTGTGTCCAGGGCCTTTG 2200	
2210 2220 2230 2240	
<u> </u>	_
CCGCCAAGCTGGATCATGTTTTAAACTCAAAAGCC 2240	
CGGAGAGATAAATGCGGGGGTTTGTGGGGGGGGTAATTCTT 2280	
CATGCAAAACAGTGGCAGGAACATTTAATACAGTACATTA 2320	,
TGGITACAATACTGTGGTCCGAATTCCAGCTGGTGCTACC 2360	
AATATIGATGTGCGGCAGCAGTTTCTCAGGGGAAACAG 2400	
2410 2420 2430 2440	
<u> </u>	
ACGATGACAACTACTTAGCTTTATCAAGCAGTAAAGGTGA 2440	
ATTCTTGCTAAATGGAAACTTTGTTGTCACAATGGCCAAA 2480	
AGGGAAATTCGCATTGGGAATGCTGTGGTAGAGTACAGTG 2520	
GGICCGAGACTGCCGTAGAAAGAATTAACTCAACAGATCG 2560	
CATTGAGCAAGAACTTTTGCTTCAGGTTTTGTCGGTGGGA 2600	
2610 2620 2630 2640	
· and the little of the little	
AAGITGTACAACCCCGATGTACGCTATTCTTTCAATATTC 2640	
CAATTGAAGATAAACCTCAGCAGTTTTACTGGAACAGTCA 2680	
TGGGCCATGCAGCAGCAGCAGCCAAGGGGAA 2720	
CGGAAACGAAAACTTGTTTGCACCAGGGAATCTGATCAGC 2760	
TTACTGTTTCTGATCAAAGATGCGATCGGCTGCCCCAGCC 2800	
2810 2820 2830 2840	
<u> </u>	
TOGACACATTACTGAACCCTGTGGTACAGGCTGTGACCTG 2840	
AGGIGGCATGITGCCAGCAGGAGTGAATGTAGTGCCCAGT 2880	
GIGGCTTGGGTTACCGCACATTGGACATCTACTGTGCCAA 2920	
ATATAGCAGGCIGGATGGGAAGACTGAGAAGGTIGATGAT 2960	
GGITTITGCAGCAGCCAACCCAAGCAAGCAACCGTGAAA 3000	

FIGURE 17 (continued)

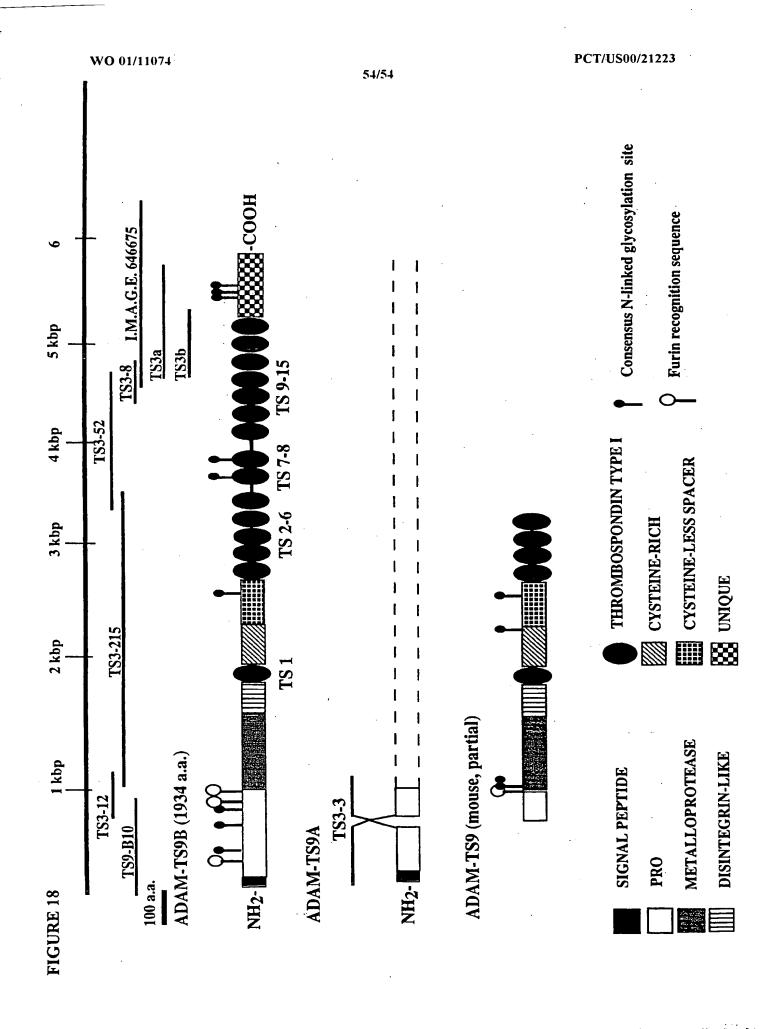
3010 3020 3030 3040 AATGCTCAGGGGAATGTAACACGGGTGGCTGGCGCTATTC 3040 TGCCTGGACTGAATGTTCAAAAAGCTGTGACGGTGGGACC 3080 CAGAGGAGAAGGCTATTTGTGTCAATACCCGAAATGATG 3120 TACTGGATGACAGCAAATGCACACATCAAGAGAAAGTTAC 3160 CATTCAGAGGIGCAGIGAGITCCCTTGICCACAGIGGAAA 3200 · 3210 3220 3230 3240 TCTGGAGACTGGTCAGAGTGCTTGGTCACCTGTGGAAAAG 3240 GCATAAGCACCGCCAGGICIGGIGICAGTTTGGIGAAGA 3280 TCGATTAAATGATAGAATGTGTGACCCTGAGACCAAGCCA 3320 ACATCTATGCAGACTTGTCAGCAGCCGGAATGTGCATCCT 3360 GGCAGGCGGICCCIGGGIACAGIGCAGIGICACTIGIGG 3400 3410 3420 3430 3440 ACAGGATACCAGCTAAGAGCAGTGAAATGCATCATTGGG 3440 ACTTATATGTCAGIGGTAGATGACAATGACTGTAATGCAG 3480 CAACTAGACCAACTGATACCCAGGACTGTGAATTACCATC 3520 ATGICATCCTCCCCAGCTGCCCCGGAAACGAGGAGAAGC 3560 ACATACAGIGCACCAAGAACCCAGIGGCGATTIGGGICIT 3600 3610 3620 3630 A CHARLES TO A CONTRACT OF THE GGACCCCATGCTCAGCCACTTGTGGGAAAGGTACCCGGAT 3640 GAGATACGICAGCIGCCGAGATGAGAATGCCICIGIGCT 3680 GACGAGAGTGCCTGCCTACCCTGCCTAGACCAGTGGCAA 3720 AGGAAGAATGTTCTGTGACACCCTGTGGGCAATGGAAGGC 3760 CTTGGACTGGAGCTCTTGCTCTGTGACCTGTGGGCCAAGGT 3800 3810 3820 3830 3840 AGGGCAACCCGGCAAGTGATGTGTGTCAACTACAGTGACC 3840 ACGICATCGAGCGAGTGAGCGACCAGGATTATATCCC 3880 AGAAACTGACCAGGACTGTTCCATGTCACCATGCCCTCAA 3920 AGGACCCCAGACAGIGGCITAGCICAGCACCCCTTCCAAA 3960 ATGAGGACTATCGTCCCCGGAGCGCCAGCCCAGCCGCAC 4000

FIGURE 17 (continued)

FIGUR	E 17 (contin	ued)			Pε
					
4010	4020	4030	4040		
ليسلسيلسن	ليتبطيين	ليستليبنا		<u> </u>	
CCATGIGCICGGIGG	AAACCAGIGC	AGAACTGGCC	CCTCG 4040		
GGAGCATGTTCCAGT	ACCIGIGCIC	ECGGATCCC	AGCGGC 4080		
GIGITGITGITATGIC	AGGATGAAAA	TGGATACACC	CCAAA 4120		
CGACTGTGTGGAGAG	SAATAAAACCI	GATGAGCAA	AGAGCC 4160		
TGTGAATCCGGCCCT	TGICCICAGI	GGGCTTATGC	CAACT 4200		
4210	4220	4230	4240		
ليستلينياسيا	ليتبيلينين	لسلسب	ــــــــــــــــــــــــــــــــــــــ		
GGGGAGAGTGCACTZ	AGCTGTGTG	TGGAGGCATZ	AAGAAC 4240		
AAGACTGGTGGTCTC	FICAGCGGICC	CAACGGIGAAC	GGTTT 4280	·	
CCAGATTIGAGCIGI	GAAATICITO	ATAAACCTC	CCGATC 4320		
GIGAGCAGIGIAACA	ACACATGCTTC	FICCACACGAC	CGCTGC 4360		
ATGGAGTACTGGCCC	TTGGAGCTCC	argricigic.	CTIGT 4400		
4410	4420	4430	4440		
لسبلسيلسب	ليبلين	<u> عبيطينين</u>	Lill	· · · · · · · · · · · · · · · · · · ·	
GGTCGAGGGCATAA	ACAACGAAAT(FITTACTGCA	rggcaa 4440		
AAGATGGAAGCCAT.	TAGAAAGIG/	ATTACTGTAA	SCACCT 4480		
GGCTAAGCCACATG	CCACAGAAA	FIGCCGAGGA	3GAAGA 4520		
TGCCCCAAATGGAA	AGCTGGCGCT.	rggagicagiy	SCICIG 4560		
TGTCCTGTGGCCGA	GCGTACAGC	AGAGGCATGT(GGCTG 4600		
4610	4620	4 630	4640	•	
سيلسيلسب	سيلسب	سيلسد	Liul		
TCAGATCGGAACAC					
AACCCATACACCAG					
GCCCACGGTGTCCCC			۵		
GCAAGAATGCACCA					
CGCAAGGIGGIGIG	IGIGGATGAC	AACAAAAACG	AGGIGC 4800		
4 810	4820	4 830	4840		
mulmulmu	Lulluu	Luuluu	Luul		
ATGGGGCACGCTGT					
TGAAAGCTGTAGTT					
ACAGGAGAATGGTC				·	
GCTACAAACAAAGG					
CGGGAAAGAGAATT	ATGAATACAG	CTACCAAACC	ACCATC 5000		

FIGURE 17 (cc nued)

5010 5020 5030 5040
AACTGCCCAGGCAGCCCCCCAGTGTTCACCCCTGTT 5040
ACCTGAGGGAGTGCCCTGTCTCGGCCACCTGGAGAGTTGG 5080
CAACIGGGGAGCIGCTCAGIGTCITGIGGIGTTGGAGIG 5120
ATGCAGAGATCTGTGCAATGTTTAACCAATGAGGACCAAC 5160
CCAGCCACTTATGCCACACTGATCTGAAGCCAGAAGAACG 5200
5210 5220 5230 5240
<u> </u>
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AATTGCAAGGAGGTAAAAAGACTTAAAGGTGCCAGTGAAG 5280
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	Ser	Arg 850	Ser	Cys	Asp	Gly	Gly 855	Thr	His	Arg	Arg	Arg 860	Ala	Ile	Сув	Val
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The second sections.

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	50 55 60 Phe Leu Leu Asn Leu Thr Arg Ser Ser Arg Leu Leu Ala Gly Arg Val	
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	Ser Val Glu Tyr Trp Thr Arg Glu Gly Leu Ala Trp Gln Arg Ala Ala 85 90 95	
	Arg Pro His Cys Leu Tyr Ala Gly His Leu Gln Gly Gln Ala Ser Ser 100 105 110	
65	Ser His Val Ala Ile Ser Thr Cys Gly Gly Leu His Gly Leu Ile Val	

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1642

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10	Thr 385	Ile	Ile	Asp	Ile	Asn 390	Gly	Thr	Val	Met	Asn 395	Tyr	Ser	Gly	Trp	Ser 400	٠
15	His	Arg	Asp	Asp	Phe 405	Leu	His	Gly	Met	Gly 410	Tyr	Ser	Ala	Thr	Lys 415	Glu	
	Ile	Leu	Ile	Val 420	Gln	Ile	Leu	Ala	Thr 425	Asp	Pro	Thr	Lys	Pro 430	Leu	Asp	
20	Val	Arg	Tyr 435	Ser	Phe	Phe	Val	Pro 440	Lys	Lys	Ser	Thr	Pro 445	Lys	Val	Asn	
	Ser	Val 450	Thr	Ser	His	Gly	Ser 455	Asn	Lys	Val	Gly	Ser 460	His	Thr	Ser	Gln	
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30	Thr	Gly	Trp	His	Thr 485	Arg	Thr	Val	Gln	Cys 490	Gln	Asp	Gly	Asn	Arg 495	Lys	
	Leu	Ala	Lys	Gly 500	Cys	Pro	Leu	Ser	Gln 505	Arg	Pro	Ser	Ala	Phe 510	Lys	Gln	
35	Cys	Leu	Leu 515	Lys	Lys	Cys											
40	<212	0> 23 L> 34 2> DN B> Ho	109	sapie	ens <i>l</i>	AD AM T	rs-10)									
45		l> CI	os 25)	. (324	10)												
)> 23 cgcac	gc c	ttco	ggto	et ca								gg a			51
50								1			•	5			5		
	atg Met 10	aga Arg	tcg Ser	cct Pro	tcc Ser	cca Pro 15	ccc Pro	gcg Ala	tgg Trp	acc Thr	aca Thr 20	acg Thr	999 Gly	cac His	tgc Cys	tgg Trp 25	99
55	cct Pro	tct Ser	cgc Arg	cac His	ctc Leu 30	ctc Leu	ccc Pro	gga Gly	gca Ala	gcg Ala 35	ccg Pro	cgg Arg	cac His	G1y 999	ggc Gly 40	cac His	147
60	agc Ser	cga Arg	gtc Val	ccg Pro 45	cct Pro	ctt Leu	cta Leu	caa Gln	agt Ser 50	ggc Gly	ctc Leu	gcc Ala	agc Ser	acc Thr 55	cac His	ttc Phe	199
65	ctg Leu	ctg Leu	aac Asn 60	ctg Leu	acc Thr	cgc Arg	agc Ser	tcc Ser 65	cgt Arg	cta Leu	ctg Leu	gca Ala	999 Gly 70	cgc Arg	gtc Val	tcc Ser	243

	gtg Val	gag Glu 75	tac Tyr	tgg Trp	aca Thr	cgg Arg	gag Glu 80	ggc	ctg Leu	gcc Ala	tgg Trp	cag Gln 85	agg Arg	gcg Ala	gcc Ala	cgg Arg	291
5	ccc Pro 90	cac His	tgc Cys	ctc Leu	tac Tyr	gct Ala 95	ggt Gly	cac His	ctg Leu	cag Gln	ggc Gly 100	cag Gln	gcc Ala	agc Ser	agc Ser	tcc Ser 105	339
10	cat His	gtg Val	gcc Ala	atc Ile	agc Ser 110	acc Thr	tgt Cys	gga Gly	ggc Gly	ctg Leu 115	cac His	ggc Gly	ctg Leu	atc Ile	gtg Val 120	gca Ala	387
15	gac Asp	gag Glu	gaa Glu	gag Glu 125	tac Tyr	ctg Leu	att Ile	gag Glu	ccc Pro 130	ctg Leu	cac His	ggt Gly	G1y 999	ccc Pro 135	aag Lys	ggt Gly	435
20	tct Ser	cgg Arg	agc Ser 140	ccg Pro	gag Glu	gaa Glu	agt Ser	gga Gly 145	cca Pro	cat His	gtg Val	gtg Val	tac Tyr 150	aag Lys	cgt Arg	tcc Ser	483
25	tct Ser	ctg Leu 155	cgt Arg	cac His	ccc Pro	cac His	ctg Leu 160	gac Asp	aca Thr	gcc Ala	tgt Cys	gga Gly 165	gtg Val	aga Arg	gat Asp	gag Glu	531
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40	gac Asp	aag Lys	atg Met 220	atg Met	gtg Val	gcc Ala	tat Tyr	cac His 225	G1y 999	cgc Arg	cgg Arg	gat Asp	gtg Val 230	gag Glu	cag Gln	tat Tyr	723
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43	cta	Gly	agc Ser	acc Thr	gtt Val	aac Asn 255	atc Ile	ctc Leu	gta Val	act Thr	cgc Arg 260	Leu	atc Ile	ctg Leu	ctc Leu	acg Thr 265	819
50	gag Glu	gac	cag Gln	ccc Pro	act Thr 270	Leu	gag Glu	atc Ile	acc Thr	cac His 275	His	gcc Ala	999 999	aag Lys	tcc Ser 280	cta Leu	867
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,,,	Leu	ato 1116 315	Th:	cgc Arg	tat Tyr	gac Asp	atc Ile 320	Cys	ato Ile	tac Tyr	aag Lys	aac Asn 325	Lys	ccc Pro	tgo Cys	ggc Gly	1011
69	aca	cta	a ggd	ctg	gco	cgg	tgg	gcg	g gaa	a tgt	gt	ago	gcg	aga	gaa	gct	1059

	Thr 330	Leu	Gly	Leu	Ala	Arg 335	Trp	Ala	Glu	Cys	Val 340	Ser	Ala	Arg	Glu	Ala 345	
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15	tgt Cys	61 Å 888	gcc Ala 380	cgt Arg	ggt Gly	cag Gln	gac Asp	cca Pro 385	gcc Ala	aag Lys	ctc Leu	atg Met	gct Ala 390	gcc Ala	cac His	att Ile	1203
	acc Thr	atg Met 395	aag Lys	acc Thr	aac Asn	cca Pro	ttc Phe 400	gtg Val	tgg Trp	tca Ser	tcc Ser	tgc Cys 405	aac Asn	cgt Arg	gac Asp	tac Tyr	1251
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25	ccc Pro	ccc Pro	aga Arg	cag Gln	gac Asp 430	ttt Phe	gtg Val	tac Tyr	ccg Pro	aca Thr 435	gtg Val	gca Ala	ccg Pro	ggc Gly	caa Gln 440	gcc · Ala	1347
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	agc Ser	aac Asn 475	cgg Arg	tgc Cys	atc Ile	acc Thr	aac Asn 480	agc Ser	atc Ile	ccg Pro	gcc Ala	gcc Ala 485	gag Glu	ggc Gly	acg Thr	ctg Leu	1491
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45	gtc Val	ccc Pro	ttt Phe	Gly 999	tcg Ser 510	cgc Arg	cca Pro	gag Glu	ggt Gly	gtg Val 515	gac Asp	gga Gly	gcc Ala	tgg Trp	999 Gly 520	ccg Pro	1587
50	tgg Trp	act Thr	cca Pro	tgg Trp 525	ggc Gly	gac Asp	tgc Cys	agc Ser	cgg Arg 530	acc Thr	tgt Cys	Gly	ggc Gly	ggc Gly 535	gtg Val	tcc Ser	1635
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65	gac Asp	agc Ser	atc Ile	cct Pro	ttc Phe 590	cgt Arg	G 1y 999	aaa Lys	ttc Phe	tac Tyr 595	aag Lys	tgg Trp	aaa Lys	acg Thr	tac Tyr 600	cgg Arg	1827

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5	aac Asn	ttc Phe	tac Tyr 620	acg Thr	gag Glu	agg Arg	gcg Ala	gca Ala 625	gcc Ala	gtg Val	gtg Val	gac Asp	630 999	aca Thr	ccc Pro	tgc Cys	1923
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40	caa Gln	ctg Leu	cga Arg	cag Gln	999 Gl <u>y</u> 750	cca Pro	gac Asp	cag Gln	gtc Val	cag Gln 755	agc Ser	ctc Leu	gaa Glu	gcc Ala	ctg Leu 760	gga Gly	2307
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. -	Pro	aaa Lys	agg Arg	Glr 845	ı Arg	g Ala	tgc Cys	aac Asr	ace Thr	Glu	cct Pro	tgc Cys	Pro	cca Pro 855	Asp	tgg Trp	2595
65	gtt	gta	a ggg	aac	tgg	tcg	cto	: tgc	ago	cgc	ago	tgc	gat	gca	ggc	gtg	2643

	Val	Val	Gly 860	Asn	Trp	Ser	Leu	Cys 865	Ser	Arg	Ser	Cys	Asp 870	Ala	Gly	Val	
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10		gcg Ala										Arg					2739
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	tgg Trp	tct Ser	gag Glu	tgc Cys 925	acc Thr	ccc Pro	agc Ser	tgc Cys	999 Gly 930	ccg Pro	ggc Gly	ctc Leu	cgc Arg	cac His 935	cgc Arg	gtg Val	2835
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25		tca Ser 955															2931
30		tgc Cys															2979
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45	Gly	cct Pro 1035				Lys					Val						3171
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60		actgo tggct					gacgo	gaged	gga	agtt	att	tatt	9998	ac o	cct	gcaggg	
		-3901	ל ככי	יצצבי	990	•										*	3409
65	<213	0 > 24 l > 10 2 > PI 3 > Ho	72 RT	sapie	ens A	ADAM?	rs-10)									

The second of the second

		> 24		Cvs	Pro	Val	Tro	Ara	Ala	Met	Ara	Ser	Pro	Ser	Pro	Pro
5	1	561	501	Cys	5	•44		5		10	5				15	
J	Ala	Trp	Thr	Thr 20	Thr	Gly	His	Cys	Trp 25	Pro	Ser	Arg	His	Leu 30	Leu	Pro
10	Gly	Ala	Ala 35	Pro	Arg	His	Gly	Gly 40	His	Ser	Arg	Val	Pro 45	Pro	Leu	Leu
	Gln	Ser 50	Gly	Leu	Ala	Ser	Thr 55	His	Phe	Leu	Leu	Asn 60	Leu	Thr	Arg	Ser
15	Ser 65	Arg	Leu	Leu	Ala	Gly 70	Arg	Val	Ser	Val	Glu 75	Tyr	Trp	Thr	Arg	Glu 80
20	Gly	Leu	Ala	Trp	Gln 85	Arg	Ala	Ala	Arg	Pro 90	His	Cys	Leu	Tyr	Ala 95	Gly
20	His	Leu	Gln	Gly 100	Gln	Ala	Ser	Ser	Ser 105	His	Val	Ala	Ile	Ser 110	Thr	Cys
25	Gly	Gly	Leu 115	His	Gly	Leu	Ile	Val 120	Ala	Asp	Glu	Glu	Glu 125	Tyr	Leu	Ile
	Glu	Pro 130	Leu	His	Gly	Gly	Pro 135	Lys	Gly	Ser	Arg	Ser 140	Pro	Glu	Glu	Ser
30	Gly 145	Pro	His	Val	Val	Tyr 150	Lys	Arg	Ser	Ser	Leu 155	Arg	His	Pro	His	Leu 160
35	Asp	Thr	Ala	Суз	Gly 165	Val	Arg	Asp	Glu	Lys 170	Pro	Trp	Lys	Gly	Arg 175	Pro
	Trp	Trp	Leu	Arg 180	Thr	Leu	Lys	Pro	Pro 185	Pro	Ala	Arg	Pro	Leu 190	Gly	Asn
40			195					200					205	Ser		
		210					215					220		Val		
45	His 225	_				230					235					240
50		Ala	Lys	Leu	Phe 245	Gln	Asp	Ser	Ser	Leu 250		Ser	Thr	Val	Asn 255	Ile
50	Leu	Val	Thr	Arg 260		Ile	Leu	Leu	Thr 265	Glu	Asp	Gln	Pro	Thr 270	Leu	Glu
55		Thr	His 275		Ala	Gly	Lys	Ser 280		Asp	Ser	Phe	Сув 285		Trp	Gln
	Lys	Ser 290		Val	Asn	His	Ser 295		His	Gly	Asn	Ala 300		Pro	Glu	Asn
60	305					310					315					Ile 320
65	_	Ile	Tyr	Lys	Asn 325		Pro	Cys	Gly	Thr 330		Gly	Leu	Ala	Arg 335	Trp
-	Ala	Glu	Cys	Val	Ser	Ala	Arg	Glu	Ala	Ala	Ala	Ser	Met	Arg	Thr	Leu

				340					345					350		
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3	Met	Asn 370	His	Asp	Gly	Val	Gly 375	Asn	Ser	Cys	Gly	Ala 380	Arg	Gly	Gln	Asp
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	Val	Trp	Ser	Ser	Cys 405	Asn	Arg	Asp	Tyr	Ile 410	Thr	Ser	Phe	Leu	Asp 415	Ser
15	Gly	Leu	Gly	Leu 420	Cys	Leu	Asn	Asn	Arg 425	Pro	Pro	Arg	Gln	Asp 430	Phe	Val
20	Tyr	Pro	Thr 435	Val	Ala	Pro	Gly	Gln 440	Ala	Tyr	Asp	Ala	Asp 445	Glu	Gln	Cys
	Arg	Phe 450	Gln	His	Gly	Val	Lys 455	Ser	Arg	Gln	Cys	Lys 460	туг	Gly	Glu	Val
25	Cys 465	Ser	Glu	Leu	Trp	Cys 470	Leu	Ser	Lys	Ser	Asn 475	Arg	Cys	Ile	Thr	Asn 480
	Ser	Ile	Pro	Ala	Ala 485	Glu	Gly	Thr	Leu	Cys 490	Gln	Thr	His	Thr	Ile 495	Asp
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	Ser	Arg 530	Thr	Cys	Gly	Gly	Gly 535	Val	Ser	Ser	Ser	Ser 540	Arg	His	Cys	Asp
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50	,		595	-		_		600			_	_	605	Lys		•
	Ser	Leu 610	Thr	Ser	Leu	Ala	Glu 615	Gly	Phe	Asn	Phe	Tyr 620	Thr	Glu	Arg	Ala
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65	Ala	Сув	Glu 675	Thr	Ile	Glu.	Gly	Val 680	Phe	Ser	Pro	Ala	Ser 685	Pro	Gly	Ala
	Gly	Tyr	Glu	Asp	Val	Val	Trp	Ile	Pro	Lys	Gly	Ser	Val	His	Ile	Phe

		690					695					700					
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	Gln	Val	Gln 755	Ser	Leu	Glu	Ala	Leu 760	Gly	Pro	Ile	Asn	Ala 765	Ser	Leu	Ile	
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	His	Tyr	Cys 835	Ser	Ala	His	Ser	Lys 840	Leu	Pro	Lys	Arg	Gln 845	Arg	Ala	Cys	
3 _. 0	Asn	Thr 850	Glu	Pro	Cys	Pro	Pro 855	Asp	Trp	Val	Val	Gly 860	Asn	Trp	Ser	Leu	
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	Cys	Pro	Pro 915	Glu	Trp	Ala	Ala	Leu 920	Asp	Trp	Ser	Glu	Cys 925	Thr	Pro	Ser	
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	Arg	Gln	Arg 995		.Val	Arg		Thr 1000		His	Thr		Gln 1005		Ser	His	
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65	102	_	Asp	Ser		Thr 1030		Gly	Asp		Pro 1035		Glu	Cys	Lys	Asp 1040	
J J	Val	Asn	Lys	Val	Ala	туг	Cys	Pro	Leu	Val	Leu	Lys	Phe	Gln	Phe	Cys	

1045

1055

1050

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	Glu	Gln	Glu 195	Asp	Glu	Glu	Glu	Gln 200	Asn	Lys	Pro	His	Ile 205	Ile	Tyr	Arq
30	Arg	Ser 210	Ala	Pro	Gln	Arg	Glu 215	Pro	Ser	Thr	Gly	Arg 220	His	Ala	Cys	Ası
35	Thr 225	Ser	Glu	His	Lys	Asn 230	Arg	His	Ser	Lys	Asp 235	Lys	Lys	Lys	Thr	Arg 240
	Ala	Arg	Lys	Trp	Gly 245	Glu	Arg	Ile	Asn	Leu 250	Ala	Gly	Asp	Val	Ala 255	Ala
40	Leu	Asn	Ser	Gly 260	Leu	Ala	Thr	Glu	Ala 265	Phe	Ser	Ala	Tyr	Gly 270	Asn	Lys
	Thr	Asp	Asn 275	Thr	Arg	Glu	Lys	Arg 280	Thr	His	Arg	Arg	Thr 285	Lys	Arg	Phe
45	Leu	Ser 290	Tyr	Pro	Arg	Phe	Val 295	Glu	Val	Leu	Val	Val 300	Ala	Asp	Asn	Arg
50	Met 305	Val	Ser	Tyr	His	Gly 310	Glu	Asn	Leu	Gln	His 315	Tyr	Ile	Leu	Thr	Le:
	Met	Ser	Ile	Val	Ala 325	Ser	Ile	Tyr	Lys	Asp 330	Pro	Ser	Ile	Gly	Asn 335	Let
55	Ile	Asn	Ile	Val 340	Ile	Val	Asn	Leu	Ile 345	Val	Ile	His	Asn	Glu 350	Gln	Asp
	Gly	Pro	Ser 355	Ile	Ser	Phe	Asn	Ala 360	Gln	Thr	Thr	Leu	Lys 365	Asn	Phe	Cys
60	Gln	Trp 370	Gln	His	Ser	Asn	Ser 375	Pro	Gly	Gly	Ile	His 380	His	Asp	Thr	Ala
65	Val 385	Leu	Leu	Thr	Arg	Gln 390	Asp	Ile	Cys	Arg	Ala 395	His	Asp	Lys	Cys	As ₁
	Thr	Lan	Clar	T.O.	λla	Glu	T.Ou	Clv	Th~	Tla	CVE	N.c.	Dro	T1	7	C

					405					410					415	
_	Cys	Ser	Ile	Ser 420	Glu	Asp	Ser	Gly	Leu 425	Ser	Thr	Ala	Phe	Thr 430	Ile	Ala
5	His	Glu	Leu 435	Gly	His	Val	Phe	Asn 440	Met	Pro	His	Asp	Asp 445	Asn	Asn	Lys
10	Cys	Lys 450	Glu	Glu	Gly	Val	Lys 455	Ser	Pro	Gln		Val 460	Met	Ala	Pro	Thr
	Leu 465	Asn	Phe	Tyr	Thr	Asn 470	Pro	Trp	Met	Trp	Ser 475	Lys	Cys	Ser	Arg	Lys 480
15	Tyr	Ile	Thr	Glu	Phe 485	Leu	Asp	Thr	Gly	Tyr 490	Gly	Glu	Cys	Leu	Leu 495	Asn
20	Glu	Pro	Glu	Ser 500	Arg	Pro	Tyr	Pro	Leu 505	Pro	Val	Gln	Leu	Pro 510	Gly	Ile
20	Leu	Tyr	Asn 515	Val	Asn	Lys	Gln	Сув 520	Glu	Leu	Ile	Phe	Gly 525	Pro	Gly	Ser
25	Gln	Val 530	Cys	Pro	Tyr	Met	Met 535	Gln	Cys	Arg	Arg	Leu 540	Trp	Ser	Asn	Asn
	Val 545	Asn	Gly	Val	His	Lys 550	Gly	Cys	Arg	Thr	Gln 555	His	Thr	Pro	Trp	Ala 560
30	Asp	Gly	Thr	Glu	Сув 565	Glu	Pro	Gly	Lys	His 570	Cys	Lys	Tyr	Gly	Phe 575	Cys
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	Trp	Ser	Pro 595	Phe	Gly	Thr	Сув	Ser 600	Arg	Thr	Cys	Gly	Gly 605	Gly	Ile	Lys
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	Tyr 625	Сув	Val	Gly	Arg	Arg 630	Met	Ĺуs	Phe	Lys	Ser 635	Cys	Asn	Thr	Glu	Pro 640
45	Cys	Leu	Lys	Gln	Lув 645	Arg	Asp	Phe	Arg	Asp 650	Glu	Gln	Cys	Ala	His 655	Phe
50	Asp	Gly	Lys	His 660	Phe	Asn	Ile	Asn	Gly 665	Leu	Leu	Pro	Asn	Val 670	Arg	Trp
	Val	Pro	Lys 675	Tyr	Ser	Gly	Ile	Leu 680	Met	Lys	Asp	Arg	Cys 685	Lys	Leu	Phe
55	Cys	Arg 690		Ala	Gly	Asn	Thr 695	Ala	Tyr	Tyr	Gln	Leu 700	Arg	Asp	Arg	Val
	705					710					715					Gln 720
60					725					730					735	Ala
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			755					760					765			
5	Val	Arg 770	Ile	Pro	Ala	Gly	Ala 775	Thr	Asn	Ile	Asp	Val 780	Arg	Gln	His	Se
	Phe 785	Ser	Gly	Glu	Thr	Asp 790	Asp	Asp	Asn	Tyr	Leu 795	Ala	Leu	Ser	Ser	Se:
10	Lys	Gly	Glu	Phe	Leu 805	Leu	Asn	Gly	Asn	Phe 810	Val	Val	Thr	Met	Ala 815	Lys
-	Arg	Glu	Ile	Arg 820	Ile	Gly	Asn	Ala	Val 825	Val	Glu	Tyr	Ser	Gly 830	Ser	Glu
15	Thr	Ala	Val 835	Glu	Arg	Ile	Asn	Ser 840	Thr	Asp	Arg	Ile	Glu 845	Gln	Glu	Let
. 20	Leu	Leu 850	Gln	Val	Leu	Ser	Val 855	Gly	Lys	Leu	Tyr	Asn 860	Pro	Asp	Val	Arg
	Tyr 865	Ser	Phe	Asn	Ile	Pro 870	Ile	Glu	Asp	Lys	Pro 875	Gln	Gln	Phe	Tyr	880
25	Asn	Ser	His	Gly	Pro 885	Trp	Gln	Ala	Cys	Ser 890	Lys	Pro	Cys	Gln	Gly 895	Glu
	Arg	Lys	Arg	Lys 900	Leu	Val	Cys	Thr	Arg 905	Glu	Ser	Asp	Gln	Leu 910	Thr	Va]
30	Ser	Asp	Gln 915	Arg	Cys	qaA	Arg	Leu 920	Pro	Gln	Pro	Gly	His 925	Ile	Thr	Glu
35	Pro	Cys 930	Gly	Thr	Gly	Cys	Asp 935	Leu	Arg	Trp	His	Val 940	Ala	Ser	Arg	Ser
	Glu 945	Cys	Ser	Ala	Gln	Cys 950	Gly	Leu	Gly	Tyr	Arg 955	Thr	Leu	Asp	Ile	Ту1 960
40	Сув	Ala	Lys	Tyr	Ser 965	Arg	Leu	Asp	Gly	Lys 970	Thr	Glu	Lys	Val	Asp 975	Asp
	Gly	Phe	Cys	Ser 980	Ser	His	Pro	Lys	Pro 985	Ser	Asn	Arg	Glu	Lys 990	Cys	Sei
15	Gly	Glu	Сув 995	Asn	Thr	Gly		Trp .000	Arg	Tyr	Ser		Trp 1005	Thr	Glu	Cys
50		Lys 1010	Ser	Cys	Asp		Gly 1015	Thr	Gln	Arg	-	Arg 1020	Ala	Ile	Cys	Va]
	Asn 1029		Arg	Asn		Val .030	Leu	Asp	Asp		Lys 1035	Сув	Thr	His		Glu .040
55	Lys	Val	Thr		Gln 1045	Arg	Cys	Ser		Phe 1050	Pro	Cys	Pro	Gln 1	Trp .055	Lys
	Ser	Gly		Trp 1060	Ser	Glu	Cys		Val 1065	Thr	Cys	Gly		Gly 1070	His	Lys
50	His		Gln 1075	Val	Trp	Cys		Phe 1080	Gly	Glu	Asp		Leu 1085	Asn	Asp ·	Arç
65		Cys 1090	Asp	Pro	Glu		Lys 1095	Pro	Thr	Ser		Gln 100	Thr	Cys	Gln	Glr
	Pro	Glu	Met	Ala	Ser	Trp	Gln	Ala	Gly	Pro	Trp	Val	Gln	Cys	Ser	Va]

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_	Thr	Cys	Gly	Gln 1	Gly 125	Tyr	Gln	Leu		Ala .130	Val	Lys	Суз		Ile 135	Gly
5	Thr	Tyr		Ser 140	Val	Val	Asp		Asn 145	Asp	Cys	Asn		Ala 150	Thr	Arg
10	Pro		Asp 155	Thr	Gln	Asp		Glu 160	Leu	Pro	Ser		His 1165	Pro	Pro	Pro
		Ala 170	Pro	Glu	Thr	_	Arg	Ser	Thr	Tyr		Ala 1180	Pro	Arg	Thr	Gln
15	Trp 1185	_	Phe	Gly		Trp 190	Thr	Pro	Cys		Ala 195	Thr	Cys	Gly		Gly .200
20	Thr	Arg	Met	Arg 1	Tyr 1205	Val	Ser	Cys		Asp .210	Glu	Asn	Gly		Val 1215	Ala
	Asp	Glu		Ala 1220	Cys	Ala	Thr		Pro 1225	Arg	Pro	Val		Lys 230	Glu	Glu
25	-	1	.235	Thr		_	1	1240	_			1	1245			
		Ser .250	Val	Thr	Cys		Gln 1255	Gly	Arg	Ala		Arg 1260	Gln	Val	Met	Cys
30	Val 1265	;	_		1	1270	٠			1	1275				. 1	280
35					1285				1	290				1	1295	
			1	Asp 1300				1	1305				1	1310		
40		1	315	Arg			:	1320					1325			
	1	.330		Arg		1	1335					1340				
45	Gly 1345	;				1350				1	1355				3	360
50					1365				1	L370				1	1375	
			1	Gly 1380					1385				1	1390		
55	•	1	.395	Leu	-	_		1400					1405			-
	3	410		Asn		:	1415				:	1420				
60	Asp 1425	5				1430					1435				1	L440
65					1445		_		1	L450				:	1455	
	Gly	Arg	Gly	His	Lys	Gln	Arg	Asn	Val	Tyr	Сув	Met	Ala	Lys	Asp	Gly

			3	460				1	465				1	4 /0		
_	Ser		Leu 475	Glu	Ser	Asp		Cys 480	Lys	His	Leu		Lys 1485	Pro	His	Gly
5	His 1	Arg 490	Lys	Суз	Arg		Gly 495	Arg	Cys	Pro		Trp .500	Lys	Ala	Gly	Ala
10	Trp 1505		Gln	Cys		Val	Ser	Cys	Gly		Gly LS15	Val	Gln	Gln		His 520
	Val	Gly	Cys		Ile 1525	Gly	Thr	His		Ile 530	Ala	Arg	Asp		Glu .535	Cys
15	Asn	Pro		Thr L540	Arg	Pro	Glu		Glu 1545	Cys	Glu	Cys		Gly 1550	Pro	Arg
20	Cys		Leu 1555	Tyr	Thr	Trp		Ala 1560	Glu	Glu	Ser		Glu 1565	Cys	Thr	Lys
20		Cys .570	Gly	Glu	Gly		Arg 1575	Tyr	Arg	Lys		Val 1580	Сув	Val	Asp	Asp
25	Asn 1585	_	Asn	Glu		His 1590	Gly	Ala	Arg		Asp L595	Val	Ser	Lys		Pro 1600
	Val	Asp	Arg		Ser 1605	Cys	Ser	Leu		Pro 1610	Cys	Glu	Tyr		Trp 1615	Ile
30	Thr	Gly		Trp 1620	Ser	Glu	Cys		Val 1625	Thr	Cys	Gly		Gly 1630	Tyr	Lys
35	Gln	_	Leu 1635	Val	Ser	Cys		Glu 1640	Ile	Tyr	Thr		Lys 1645	Glu	Asn	Tyr
32		Tyr 1650	Ser	Tyr	Gln		Thr 1655	Ile	Asn	Cys		Gly 1660	Thr	Gln	Pro	Pro
40	Ser 1665		His	Pro		Tyr 1670	Leu	Arg	Glu		Pro 1675	Val	Ser	Ala		Trp 1680
	Arg	Val	Gly		Trp 1685	Gly	Ser	Cys		Val 1690	Ser	Cys	Gly		Gly 1695	Val
45	Met	Gln		Ser 1700	Val	Gln	Сув		Thr 1705	Asn	Glu	Asp		Pro 1710	Ser	His
50	Leu		His 1715		Asp	Leu		Pro 1720	Glu	Glu	Arg		Thr 1725	Cys	Arg	Asr
		Tyr 1730		Сув	Glu		Pro 1735	Gln	Asn	Сув		Glu 1740	Val	Lys	Arg	Let
55	Lys 174	-	Ala	Ser		Asp 1750		Glu	Tyr		Leu 1755	Met	Ile	Arg		Lys 1760
	Leu	Leu	Lys		Phe 1765		Ala	Gly		His 1770		Asp	His		Lys 1775	Glı
60	Tyr	Val	Thr	Leu 1780		His	Gly		Ser 1785		Asn	Phe		Glu 1790	Val	Ту
65	-	His	Arg 1795		His	Asn		Thr 1800		Суѕ	Pro	Tyr	Asn 1805		Ser	Arg
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1810 1815 1820

Ser Phe Gln Lys Ile Arg Ile Asp Leu Thr Ser Met Gln Ile Ile Thr 1825 1830 1835 1840

Thr Asp Leu Gln Phe Ala Arg Thr Ser Glu Gly His Pro Val Pro Phe 1845 1850 1855

Ala Thr Ala Gly Asp Cys Tyr Ser Ala Ala Lys Cys Pro Gln Gly Arg 10 1860 1865 1870

Phe Ser Ile Asn Leu Tyr Gly Thr Gly Leu Ser Leu Thr Glu Ser Ala 1875 1880 1885

15 Arg Trp Ile Ser Gln Gly Asn Tyr Ala Val Ser Asp Ile Lys Lys Ser 1890 1895 1900

Pro Asp Gly Thr Arg Val Val Gly Lys Cys Gly Gly Tyr Cys Gly Lys 1905 1910 1915 1920

20 Cys Thr Pro Ser Ser Gly Thr Gly Leu Glu Val Arg Val Leu 1925 1930

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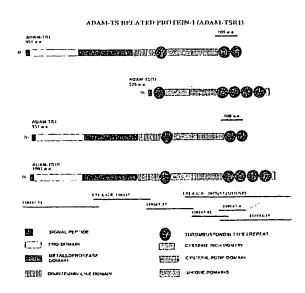
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(54) Title: NUCLEIC ACIDS ENCODING ZINC METALLOPROTEASES



(57) Abstract: Isolated mammalian proteins having disintegrin-like and metalloprotease domains with thrombospondin type I motifs, i.e., ADAMTS proteins, are provided. The proteins are ADAMTS-5, ADAMTS-6, ADAMTS-7, ADAMTS-8, ADAMTS-9 and ADAMTS-10, collectively referred to as "ADAMTS-N". The present invention also provides isolated polynucleotides which encode an ADAMTS-N protein or a variant thereof, polynucleotide sequences complementary to such polynucleotides, vectors containing such polynucleotides, and host cells transformed or transfected with such vectors. The present invention also relates to antibodies which are immunospecific for one or more of the ADAMTS-N proteins. The present invention also relates to a protein referred to hereinafter as ADAMTS-R1 (ADAM-TS Related protein-1) and the polynucleotides which encode such protein.



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NUCLEIC ACIDS ENCODING ZINC METALLOPROTEASES

Background of the Invention

This invention relates to isolated nucleic acid -molecules

which encode proteins belonging to a zinc metalloprotease family.

The zinc metalloproteases have been implicated in a variety of diseases and development disorders that involve* enhanced or depressed proteolysis of components of the extracellular matrix, receptors, or other extracellular molecules.

More particularly, the invention relates to isolated nucleic acid molecules encoding proteins belonging to a subfamily of zinc metalloproteases referred to as "ADAMTS", an abbreviation for A Disintegrin-like And Metalloprotease domain with ThromboSpondin type I motifs. Proteins in the ADAMTS subfamily all possess a Zn protease catalytic site consensus sequence (HEXXH+H), which suggests an intact catalytic activity for each of these proteins. The ADAMTS proteins also have putative N-terminal signal peptides and lack transmembrane domains, which suggests that the proteins in this subfamily are secreted. The proteins in the ADAMTS subfamily also possess at least one thrombospondin type (TSP1) motif, which suggests a binding of these proteins to components of the extracellular matrix (ECM) or to cell surface components.

Members of the ADAMTS subfamily of proteins are ADAMTS-1,
ADAMTS-2, ADAMTS-3, and ADAMTS-4. ADAMTS-1 protein is selectively
25 expressed in colon 26 adenocarcinoma cachexigenic sublines. ADAMTS-1
mRNA is induced by the inflammatory cytokine interleukin-1 in vitro
and by intravenous administration of lipopolysaccharide in vivo.
Thus, the ADAMTS-1 protein is believed to play a role in tumor
cachexia and inflammation.

The ADAMTS-2 protein is also known as procollagen I/H aminopropetide processing enzyme or PCINP. The ADAMTS-2 protein catalyzes cleavage of native triple-helical procollagen I and procollagen II.

The ADAMTS-2 protein also has an affinity for collagen XIV. Lack of the ADAMTS-2 protein is known to cause dermatosparaxis in cattle, or Ehlers-Danlos syndrome type VIIC (EDS-VIIC) in humans. EDS-VIIC is 5 characterized clinically by severe skin fragility, and biochemically by the presence in skin of procollagen which is incompletely processed at the amino terminus. Thus, it is believed that the ADAMTS-2 protein plays a role in processing of procollagen to mature collagen, an essential step for correct assembly of collagen into
10 collagen fibrils. The ADAMTS-3 protein is similar in sequence to ADAMTS-2 and may have similar function.

The ADAMTS-4 protein catalyzes cleavage of the core protein of the extracellular matrix proteoglycan, aggrecan. Aggrecan degradation is an important factor in the erosion of articular cartilage in arthritic disease. Aggrecan fragments have been identified in cultures undergoing cartilage matrix degradation and in arthritic synovial fluids. Therefore, overexpression or activation 10 of ADAMTS-4 protein may be related to both inflammatory and non-inflammatory arthritis.

- On the basis of the structure, location, and the demonstrated proteolytic activity of ADAMTS proteins 1-4, it is expected that other members of the ADAMTS subfamily play a role in the cleavage of proteoglycan core proteins that are found in the extracellular matrix, such as, for example, versican, brevican, neuracan, NG-2,
- 25 aggrecan, as well as molecules such as collagen. It is also expected that other members of the ADAMTS subfamily play a role in embryogenesis, implantation of a fertilized egg, angiogenesis, arthritic degradation of cartilage, inflammation, nerve regeneration, tumor growth, and metastases.
- 30 Thus, it is desirable to have other members of the ADAMTS

subfamily of proteins, the nucleic acids that encode such proteins, and antibodies that are specific for such proteins. Such molecules are useful research tools for studying development of the extracellular matrix during embryogenesis and fetal development, and for studying disorders or diseases that are characterized by improper development of the extracellular matrix or enhanced or reduced destruction of the extracellular matrix. Such molecules, particularly the nucleic acids and the antibodies, are also useful tools for diagnosing such diseases or for monitoring the efficacy of therapeutic agents that have been developed to treat such diseases.

Summary of the Invention

The present invention provides novel, isolated, and substantially purified proteins having the characteristics of an 15 ADAMTS protein. The novel proteins are referred to hereinafter individually as "ADAMTS-5", "ADAMTS-6", "ADAMTS-7", "ADAMTS-8", "ADAMTS-9" and "ADAMTS-10", and collectively as "ADAMTS-N". In one embodiment, the ADAMTS-5 protein is a mature mouse protein which comprises amino acid 231 through amino acid 930 of the sequence set 20 forth set forth in SEQ ID NO: 2. In another embodiment, ADAMTS-5 is a human ADAMTS-5 protein which comprises amino acid 1 through amino acid 518 of the sequence set forth in SEQ ID NO: 4. In one embodiment, mature human ADAMTS-6 protein comprises amino acid 245 through amino acid 860 of SEQ ID NO: 6. In one embodiment, mature 25 human ADAMTS-7 protein comprises amino acid 233 through amino acid 997 of the sequence set forth in SEQ ID NO: 8. In one embodiment, mature ADAMTS-8 protein is a mouse protein which comprises amino acid 229 through amino acid 905 of the sequence set forth in SEQ ID NO: 10. In another embodiment, ADAMTS-8 protein is a human protein which 30 comprises amino acid 1 through amino acid 245 of the sequence set forth in SEQ ID NO: 12. In one embodiment, mature ADAMTS-9 protein

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is a human protein which comprises amino acid 236 through amino acid 1882 of the sequence set forth in SEQ ID NO: 14. In another embodiment, ADAMTS-9 protein is a mouse protein which comprises amino acid 1 through amino acid 974 of the sequence set forth in SEQ ID NO:

- 5 16. In one embodiment, mature ADAMTS 10 protein is a human protein which comprises amino acid 212 through amino acid 1081 of the sequence set forth in SEQ ID NO: 18. In another embodiment, ADAMTS-10 protein is a mouse protein which comprises amino acid 1 through amino acid 547 of the sequence set forth in SEQ ID NO: 20.
- The present invention also provides isolated polynucleotides which encode an ADAMTS-N protein or a variant thereof, polynucleotide sequences complementary to such polynucleotides, vectors containing such polynucleotides, and host cells transformed or transfected with such vectors. The present invention also relates to antibodies which are immunospecific for one or more of the ADAMTS-N proteins. The
 - present invention also relates to a protein referred to hereinafter as ADAMTS-R1 (ADAM-T-S Related protein-1) and the polynucleotides which encode such protein. In one embodiment, the ADAMTS-R1 protein comprises amino acid 1 through amino acid 525 of the sequence set
- 20 forth in SEQ. ID NO: 22.

Brief Description of the Drawings
Figure 1 shows an amino acid sequence (SEQ ID NO:2) of a full-length
mouse ADAMTS-5 protein and a nucleic acid sequence (SEQ ID NO: 1)
which encodes such protein.

25 Figure 2 shows an amino acid sequence (SEQ ID NO:4) of a partial human ADAMTS-5 protein and a nucleic acid sequence (SEQ ID NO: 3) which encodes such protein.

Figure 3 shows an amino acid sequence (SEQ ID NO:6) of a full-length human ADAMTS-6 protein and a nucleic acid sequence (SEQ ID NO:5)

30 which encodes such protein.

Figure 4 shows an amino acid sequence (SEQ ID NO:8) of a full-length human ADAMTS-7 protein and a nucleic acid sequence (SEQ ID NO:7) which encodes such protein.

Figure 5 shows an amino acid sequence (SEQ ID NO: 10) of a full-

5 length mouse ADAMTS-8 protein and a nucleic acid sequence (SEQ ID NO:9) which encodes such protein.

Figure 6 shows an amino acid sequence (SEQ ID NO: 12) of a partial human ADAMTS-8 protein and a nucleic acid sequence (SEQ ID NO: 11) which encodes such amino acid sequence.

10 Figure 7 shows an amino acid sequence (SEQ ID NO: 14), of a full-length human ADAMTS-9 protein and a nucleic acid sequence (SEQ ID NO: 13) Which encodes such protein.

Figure 8 shows an amino acid sequence (SEQ ID NO: 16) of a partial mouse ADAMTS-9 protein and a nucleic acid sequence (SEQ ID NO: 15)

15 which encodes such amino acid sequence.

Figure 9 shows an amino acid sequence (SEQ ID NO:18) of a full-length human ADAMTS-10 protein and a nucleic acid sequence (SEQ ID NO: 17) which encodes such protein.

Figure 10 show's an amino acid sequence (SEQ ID NO:20) of a partial 20 mouse ADAMTS-10 protein and a nucleic acid sequence (SEQ ID NO: 19) which encodes such amino acid sequence.

Figure 11 shows an amino acid sequence (SEQ ID NO:22) of a full length ADAMTS-R1 protein and a nucleic acid sequence (SEQ ID NO: 21) which encodes such protein.

25 Figure 12 depicts the cloning strategy used for isolation of a. mouse and human ADAMTS-5 cDNAs b. human ADAMTS-6 cDNA and c. human ADAMTS-7 cDNA. The domain organization of each protein relative to the cDNA clones (thin line) is shown as is the extent of overlap between clones. The original I.M.A.G.E. clones are underlined. Intronic 30 regions of incompletely spliced transcripts are shown by the angled

and the state of the state of

dotted lines. DNA scale marker (in bp) and amino acid scale marker are at upper right. Location of the probe used for in situ hybridization (ISH) is shown in a.

Figure 13 shows the predicted amino acid sequences of a. the mouse 5 and human ADAMTS-5 proteins (alignment shows mouse sequence above, partial human sequence below) b. ADAMTS-6, and c. ADAMTS-7. The active-site sequences and proposed Met-turn are enclosed in boxes.

Potential furin cleavage site(s) are indicated by arrows.

Thrombospondin type-1 modules are underlined. Potential sites for N-

- 10 inked glycosylation are overlined. Cysteine residues within the context of an MMP-like "cysteine switch" are indicated by the solid circles. Other cysteine residues are indicated by asterisks. The prodomain extends until the furin cleavage site, and the catalytic domain extends from the furin cleavage site to the approximate start
- 15 of the disintegrin-like sequence (Dis). The start of the spacer domain is indicated; the region between the N-terminal TS domain and the spacer domain is the cysteine-rich domain. The single letter amino acid code is used.

Figure 14 shows Northern analysis of expression of ADAMTS-5, 6 and 7.

- 20 RNA kilobase markers are shown at left of each autoradiogram, and tissue origin is indicated above each lane. a. Mouse embryo northern blots. b. Human multiple adult tissue northern blots.
 - Figure 15 is a schematic representation of the domain structure of ADAMTS-R1 protein as compared to ADAMTS-1 protein.
- 25 Figure 16 shows an amino acid sequence (SEQ ID NO: 24) of an alternative embodiment of a full-length human ADAMTS-10 protein and a nucleic acid sequence (SEQ ID NO: 23) which encodes such protein.

 Figure 17 shows an amino acid sequence (SEQ ID NO: 26) of an alternative embodiment of human ADAMTS-9, which is a full-length

 30 protein designated as human ADAMTS-9b and a nucleic acid sequence

(SEQ ID NO: 25) which encodes such protein.

Figure 18 is a schematic representation of the domain structure of human ADAMTS-9b protein as compared to human and mouse ADAMTS-9 protein.

Detailed Description of the Invention

The present invention relates to novel, isolated, substantially purified, mammalian proteins belonging to the ADAMTS subfamily of metalloproteases. As used herein, the term "substantially purified" 10 refers to a protein that is removed from its natural environment, isolated or separated, and at least 60% free, preferably 75% free, and most preferably 90% free from other components with which it is naturally associated.

The novel mammalian proteins are ADAMTS-5, ADAMTS-6, ADAMTS-7, 15 ADAMTS-8, ADAMTS-9 and ADAMTS-10, collectively ADAMTS-N. In one embodiment, the ADAMTS-5 protein is a mature mouse protein which comprises amino acid 231 through amino acid 930 of the sequence set forth in SEQ ID NO: 2. In another embodiment, the ADAMTS-5 protein is a human protein which comprises amino acid 1 through amino acid 20 518 of the sequence set forth in SEQ ID NO: 4. In one embodiment, ADAMTS-6 protein is a mat-Lire human protein which comprises amino acid 245 through amino acid 860 of SEQ ID NO:6. In one embodiment, the ADAMTS-7 protein is a mature human protein which comprises amino acid 233 through amino acid 997 of the sequence set forth in SEQ ID 25 NO: 8. In one embodiment, the ADAMTS-8 protein is a mature mouse protein which comprises amino acid 229 through amino acid 905 of the sequence set forth in SEQ ID NO: 10. In another embodiment, the ADAMTS-8 protein is a human protein which comprises amino acid 1 through amino acid 245 of the sequence set forth in SEQ ID NO: 12. 30 In one embodiment, the ADAMTS-9 is a mature human protein which comprises amino acid 236 through amino acid 1882 of the sequence set

forth in SEQ ID NO: 14. In another embodiment, the ADAMTS-9 protein is a mouse protein which comprises amino acid 1 through amino acid 874 of the sequence set forth in SEQ ID NO: 16. In another embodiment, the ADAMTS-9 designated ADAMTS-9b is a human protein 5 which is comprised of 1934 amino acids as set forth in SEQ ID NO 26. In one embodiment, the ADAMTS-10 protein is a mature human protein which comprises amino acid 212 through amino acid 1081 of the sequence set forth in SEQ ID NO: 18. In another embodiment the ADAMTS- 10 protein is a mouse protein which comprises amino acid 1.

10 through amino acid 525 of the sequence set forth in SEQ ID NO:20. In another embodiment, the ADAMTS-10 protein is a human protein which is comprised of 1072 amino acids as set forth in SEQ ID NO 24.

All of the novel ADAMTS-N proteins starting at the amino terminus comprise a signal sequence followed by a putative pro region 15 which contains a consensus sequence for furin cleavage (except for ADAMTS-10), a catalytic domain, a domain of 60-90 residues with 35 to 45% similarity to snake venom disintegrins, a TS module, a cysteine rich domain containing multiple conserved cysteine residues, a spacer domain, and one or multiple C terminal TS modules. (See Figure 12.)

20 As determined using the BLAST software from the National Center for Biotechnology Information, the predicted mature forms of the ADAMTS-N proteins show an overall 20-30% similarity to each other and to ADAMTS-1-4, although this may be considerably higher or lower for individual domains as described below.

25 The ADAMTS-N proteins also encompass variants of the ADAMTS-N proteins shown in Figs. 1-10. A "variant" as used herein, refers to a protein whose amino acid sequ nce is similar to one of the amino acid sequences shown in Figs. 1-10, hereinafter referred to as the reference amino acid sequence, but does not have 100% identity with 30 the reference sequence. The variant protein has an altered sequence

in which one or more of the amino acids in the reference sequence is deleted or substituted, or one or more amino acids are inserted into the sequence of the reference amino acid sequence. As a result of the alterations, the variant protein has an amino acid sequence which 5 is at least 95% identical to the reference sequence, preferably, at least 97% identical, more preferably at least 98% identical, most preferably at least 99% identical to the reference sequence. Variant sequences which are at least 95% identical have no more than 5 alterations, i.e. any combination of deletions, insertions or 10 substitutions, per 100 amino acids of the reference sequence. Percent identity is determined by comparing the amino acid sequence of the variant with the reference sequence using MEGALIGN project in the DNA STAR program. Sequences are aligned for identity calculations using the method of the software basic local alignment 15 search tool in the BLAST network service (the National Center for Biotechnology Information, Bethesda, MD) which employs the method of Altschul, S. F., Gish, W., Miller, W., Myers, E. W. & Lipman, D. J. (1990) J. Mol. Biol. 215, 403-410. Identities are calculated by the Align program (DNAstar, Inc.) In all cases, internal gaps and amino 20 acid insertions in the candidate sequence as aligned are not ignored when making the identity calculation.

while it is possible to have nonconservative amino acid substitutions, it is preferred that the substitutions be conservative amino acid substitutions, in which the substituted amino acid has similar structural or chemical properties with the corresponding amino acid in the reference sequence. By way of example, conservative amino acid substitutions involve substitution of one aliphatic or hydrophobic amino acids, e.g. alanine, valine, leucine and isoleucine, with another; substitution of one hydroxyl-containing amino acid, e.g. serine and threonine, with another; substitution of

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one acidic residue, e.g. glutamic acid or aspartic acid, with another; replacement of one amide-containing residue, e.g. asparagine and glutamine, with another; replacement of one aromatic, residue, e.g. phenylalanine and tyrosine, with another; replacement of one basic residue, e.g. lysine, arginine and histidine, with another; and replacement of one small amino acid, e.g., alanine, serine, threonine, methionine, and glycine, with another.

The alterations are designed not to abolish the immunoreactivity of the variant protein with antibodies that bind to the reference protein. Guidance in determining which amino acid residues may be substituted, inserted or deleted without abolishing immunoreactivity of the variant protein with an antibody specific for the respective reference protein are found using computer programs well known in the art, for example, DNASTAR software.

The ADAMTS-N proteins also encompass fusion proteins comprising an ADAMTS-N protein and a tag, i.e., a second protein or one or more amino acids, preferably from about 2 to 65 amino acids, more preferably from about 34 to about 62 amino acids, which are added to the amino terminus of, the carboxy terminus of, or any point within 20 the amino acid sequence of an ADAMTS-N protein, or a variant of such protein. Typically, such additions are made to stabilize the resulting fusion protein or to simplify purification of an expressed recombinant form of the corresponding ADAMTS-N protein or variant of such protein. Such tags are known in the art. Representative 25 examples of such tags include sequences which encode a series of histidine residues, the epitope tag FLAG, the Herpes simplex glycoprotein D, beta-galactosidase, maltose binding protein, or glutathione S-transferase.

The ADAMTS-N proteins also encompass ADAMTS-N proteins in which 30 one or more amino acids, preferably no more than 10 amino acids, in

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the respective ADAMTS-N protein are altered by posttranslation processes or synthetic methods. Examples of such modifications include, but are not limited to, acetylation, amidation, ADP-ribosylation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or a lipid, cross-linking gamma-carboxylation, glycosylation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, sulfation, and transfer-RNA mediated additions of amino acids to proteins such as arginylation and ubiquitination.

The ADAMTS-N proteins are immunogenic and, thus, are useful for preparing antibodies. Such antibodies are useful for identifying and diagnosing disorders which are associated with decreased expression or activity or increased expression of an ADAMTS-N protein. The 15 ADAMTS-N protein may also be useful for treating such disorder.

Diseases involving enhanced or depressed proteolyisis of the core proteins of the extracellular may involve enhanced expression or activity or decreased expression or activity of one or more ADAMTS-N proteins. Thus, ADAMTS-N proteins may be used to identify drugs,

20 polypeptides, auto-antibodies, or other natural compounds which bind to an ADAMTS-N protein with sufficient affinity to block or facilitate its activity. The activity of the ADAMTS-N protein is assayed in the presence and the absence of the putative inhibitor or facilitator using any of a variety of protease assays known in the

25 art. In general, the activity of the ADAMTS-N protein is assayed through the use of a peptide or protein substrate having a known or putative cleavage site for the ADAMTS-N protein. To detect cleavage or to monitor the extent of cleavage, the substrate is tagged in a manner which provides a detectable signal upon cleavage. For

side of the cleavage site and with a fluorescence-quenching group on the opposite side of the cleavage site. Upon cleavage by the substrate, quenching is eliminated and a detectable signal is produced. Alternatively, the substrate is tagged with a colorimetric leaving group that more strongly absorbs upon cleavage. Agents which block ADAMTS-N-catalyzed cleavage of a protein substrate may be administered to a subject to block proteolysis of the corresponding protein substrate.

ADAMTS-R1 Protein

- The present invention also relates to a protein, referred to hereinafter as "ADAMTS-R1". From its amino to its carboxyl terminus, ADAMTS-R1 comprises a signal peptide sequence, a TS1 module, a cysteine-rich domain, a spacer domain, and three TS1 modules. Thus, ADAMTS-R1 has a structure which is related to or similar to an
- 15 ADAMTS-N protein, but which lacks a catalytic domain and a disintegrin-like domain. In one embodiment, ADAMTS-R1, protein comprises amino acid 1 through amino acid 525 of the amino acid sequence, SEQ ID N0:22, shown in Fig. 11. Such protein has a 30-40% overall sequence identity with similar regions of the ADAMTS-N
- 20 proteins. The ADAMTS-R1 proteins also encompass variants of the amino acid sequence shown in Fig. 11 and fusion proteins which contain the amino acid sequence shown in Fig. 11 or a variant thereof. On the basis of its domain organization, it is expected that ADAMTS-R1 can bind to extracellular matrix or cell surface
- 25 molecules, including ADAMTS-N substrates. Thus, it is expected that ADAMTS-R1 can be used as an cell-matrix or cell-cell adhesion molecule or an ADAMTS-N competitive inhibitor. The ADAMTS-R1 proteins are also useful for preparing antibodies. Such antibodies are useful for identifying tissues where ADAMTS-R1 is expressed and 30 for diagnosing disorders which are associated with decreased

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expression or increased expression of. an ADAMTS-R1 protein.

Polynucleotides

The present invention also provides isolated polynucleotides which encode the mammalian ADAMTS-N proteins and the mammalian

- 5 ADAMTS-R1 protein. Figure 1 shows one embodiment of a polynucleotide, SEQ ID NO: 1, which encodes the full-length mouse ADAMTS-5 protein. Figure 2 shows one embodiment of a polynucleotide; SEQ ID NO: 3, which encodes a partial human ADAMTS-5 protein. Figure 3 shows one embodiment of a polynucleotide; SEQ ID NO: 5, which
- 10 encodes a full-length human ADAMTS-6 protein. Figure 4 shows one embodiment of a polynucleotide; SEQ ID NO: 7, which encodes a full-length human ADAMTS-7 protein. Figure 5 shows one embodiment of a polynucleotide; SEQ ID NO: 9, which encodes a full-length mouse ADAMTS-8 protein. Figure 6 shows one embodiment of a polynucleotide;
- 15 SEQ ID NO: 11, which encodes a partial human ADAMTS-8 protein.

 Figure 7 shows one embodiment of a polynucleotide; SEQ ID NO: 13,

 which encodes a full-length human ADAMTS-9 protein. Figure 8 shows

 one embodiment of a polynucleotide; SEQ ID NO: 15, which encodes a

 partial ADAMTS-9 protein. Figure 9 shows one embodiment of a
- 20 polynucleotide; SEQ ID NO: 17, which encodes a full-length human ADAMTS-10 protein. Figure 10 shows one embodiment of a polynucleotide; SEQ ID NO: 19, which encodes a partial mouse ADAMTS-10 protein. Figure 11 shows one embodiment of a polynucleotide; SEQ ID NO: 21, which encodes a full-length ADAMTS-R1 protein.
- Due to the known degeneracy of the genetic code wherein more than one codon can encode the same amino acid, a DNA sequence may vary from that shown in SEQ ID NO: 1 and still encode an ADAMTS-5 protein having the amino acid sequence of SEQ ID NO: 2. Similarly, a DNA sequence may vary from that shown in SEQ ID NO:5, and still so encode an ADAMTS-6 protein having the amino acid sequence set forth

in SEQ ID NO:6. Similarly a DNA sequence may vary from that shown in SEQ ID NOS: 7, 9, 11, and 13, and still encode the amino acid sequences shown in SEQ ID NOS: 8, 10, 12, and 14, respectively.

Such variant DNA sequence may result from silent mutations, such as for example those that occur during PCR amplification or from deliberate mutagenesis of a native sequence.

The present polynucleotides also encompass polynucleotides having sequences that are capable of hybridizing to the nucleotide sequences of FIGS 1 - 11 under stringent conditions, preferably 10 highly stringent conditions. Hybridization conditions are based on the melting temperature™ of the nucleic acid binding complex or probe, as described in Berger and Kimmel (1987) Guide to Molecular Cloning Techniques, Methods in Enzymology, vol 152, Academic Press. The term "stringent conditions, as used herein, is the "stringency" 15 which occurs within a range from about Tm-5 (5° below the melting temperature of the probe) to about 20° C below Tm. As used herein "highly stringent" conditions employ at least 0.2 x SSC buffer and at least 65° C. As recognized in the art, stringency conditions can be attained by varying a number of factors such as the length and 20 nature, i.e., DNA or RNA, of the probe; the length and nature of the target sequence, the concentration of the salts and other components, such as formamide, dextran sulfate, and polyethylene glycol, of the hybridization solution. All of these factors may be varied to generate conditions of stringency which are equivalent to the 25 conditions listed above.

The present polynucleotides also encompasses alleles of the ADAMTS-N and ADAMTS-R1 encoding sequences. As used herein, an allele or allelic sequence is an alternative form of an ADAMTS-N or ADAMTS-R1 encoding sequence which is present at the same gene locus. The 30 allele may result from one or more mutations in the ADAMTS-N or

ADAMTS-R1 encoding sequence. Such mutations typically arise from natural addition, deletion of substitution of nucleotides in the open reading frame sequences. Any gene which encodes an ADAMTS-N protein or ADAMTS-RI protein may have none, one, or several allelic forms.

5 Such alleles are identified using conventional techniques, such as for example screening, libraries with probes having sequences identical to or complementary with one or more ADAMTS-N polynucleotides.

The present polynucleotides also encompass altered

10 polynucleotides which encode ADAMTS-N proteins, ADAMTS-R1 proteins, and variants thereof. Such alterations include deletions, additions, or substitutions. Such alterations may produce a silent change and result in an ADAMTS-N protein having the same amino acid sequence as the ADAMTS-N protein encoded by the unaltered polynucleotide. Such 15 alterations may produce a nucleotide sequence possessing nonnaturally occurring codons. For example, codons preferred by a particular prokaryotic or eucaryotic host may be incorporated into the nucleotide sequences showing Figures 1 -11 to increase the rate of expression of the proteins encoded by such sequences. Such 20 alterations may also introduce new restriction sites into the sequence or result in the production of an ADAMTS-N or ADAMTS-RI variant. Typically, such alterations are accomplished using sitedirected mutagenesis.

The polynucleotides are useful for producing ADAMTS-N or

25 ADAMTS-R1 proteins. For example, an RNA molecule encoding an ADAMTSN protein is used in a cell-free translation systems to prepare such
protein. Alternatively, a DNA molecule encoding an ADAMTS-N protein
is introduced into an expression vector and used to transform cells.
Suitable expression vectors include for example chromosomal,

30 nonchromosomal and synthetic DNA sequences, e.g., derivatives of

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SV40, bacterial plasmids, phage DNAs; yeast plasmids, vectors derived from combinations of plasmids and phage DNAs, viral DNA such as vaccinia, adenovirus, fowl pox virus, pseudorabies, baculovirus, and retrovirus. The DNA sequence is introduced into the expression 5 vector by 5 conventional procedures.

Accordingly, the present invention also relates to recombinant constructs comprising one or more of the present polynucleotide sequences. Suitable constructs include, for example, vectors, such as a plasmid, phagemid, or viral vector, into which a sequence that, 10 encodes an ADAMTS-N protein or an ADAMTS-R1 protein has been inserted. In the expression vector, the DNA sequence which encodes the ADAMTS-N protein is operatively linked to an expression control sequence, i.e., a promoter, which directs mRNA synthesis. Representative examples of such promoters, include the LTR or SV40 15 promoter, the E. coli lac or trp, the phage lambda PL promoter and other promoters known to control expression of genes in prokaryotic or eukaryotic cells or in viruses. The promoter may also be the . natural promoter of the ADAMTS-N encoding sequence. The expression vector, preferably, also contains a ribosome binding site for 20 translation initiation and a transcription terminator. Preferably, the recombinant expression vectors also include an origin of replication and a selectable marker, such as for example, the ampicillin resistance gene of E. coli to permit selection of transformed cells, i.e. cells that are expressing the heterologous 25 DNA sequences. The polynucleotide sequence encoding the ADAMTS-N

The polynucleotides encoding an ADAMTS-N or ADAMTS-R1 protein are used to express recombinant protein using techniques well known 30 in the art. Such techniques are described in Sambrook, J. et al

protein is incorporated into the vector in frame with translation

initiation and termination sequences.

(1989) Molecular Cloning A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y. and Ausubel, F. M. et al. (1989) Cuurent Protocols in Molecular Biology, John Wile & Sons, New York, NY.

Polynucleotides encoding an ADAMTS-N or ADAMTS-R1 protein may

5 also be used for diagnostic purposes. The polynucleotides may be
used to detect and quantify ADAMTS-N or ADAMTS-R1 gene transcripts in
biopsied tissues in which enhanced expression or reduced expression
of the corresponding ADAMTS-N or ADAMTS-RI gene is correlated with a
disease. The diagnostic assay may be used to determine whether

10 expression is absent, present, or altered and to determine whether
certain therapeutic agents modulate expression of the corresponding
ADAMTS-N or ADAMTS-R1 gene.

Also encompassed by the present invention, are single stranded polynucleotides, hereinafter referred to as antisense

15 polynucleotides, having sequences which are complementary to the DNA and RNA sequences which encode the ADAMTS-N or ADAMTS-R1 proteins.

The term complementary as used herein refers to the natural binding of the polynucleotides under permissive salt and 5 temperature conditions by base pairing.

- The present invention also encompasses oligonucleotides that are used as primers in polyrnerase chain reaction (PCR) technologies to amplify transcripts of the genes which encode the ADAMTS-N and ADAMTSR-1 proteins or portions of such transcripts. Preferably, the primers comprise 18-30 nucleotides, more preferably 19-25
- 25 nucleotides. Preferably, the primers have a G+C content of 40% or greater. Such oligonucleotides are at least 98% complementary with a portion of the DNA strand, i.e., the sense strand, which encodes the respective ADAM-TS family protein or a portion of its corresponding antisense strand. Preferably, the primer has at least 99%

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sense strand or its corresponding antisense strand. Primers which are which have 100% complementarity with the antisense strand of a double-stranded DNA molecule which encodes an ADAMTS-N protein have a sequence which is identical to a sequence contained within the sense 5 strand. The identity of primers which are 15 nucleotides in length and have full complementarity with a portion of the antisense strand of a double-stranded DNA molecule which encodes the ADAMTS-N protein is determined using the nucleotide sequences, shown in FIG I - 11 and described by the general formula a-b; where a is any integer between 10 I and the position number of the nucleotide which is located 15 residues upstream of the 3' end of the sense or antisense strand of the cDNA sequences shown in FIG 1 -11; where b is equal to a+14; and where both a and b correspond to the positions of nucleotide residues of the cDNA sequences shown in FIGS 1 - 11.

- The present invention also encompasses oligonucleotides that are useful as hybridization probes for for isolating and identifying cDNA clones and genomic clones encoding the ADAMTS-N or ADAMTS-R1 protein or allelic forms thereof. Such hybridization probes are also useful for detecting transcripts of the genes which encode the ADAMTS-N family proteins or for mapping of the genes which encode the ADAMTS-N proteins Preferably, such oligonucleotides comprise at least 210 nucleotides, more preferably at least 230, most preferably from about 210 to 280 nucleotides. Such hybridization probes have a sequence which is at least 90% complementary with a sequence 25 contained within the sense strand of a DNA molecule which encodes an ADAMTS-N protein or ADAMTS-P1 protein or with a sequence contained
- ADAMTS-N protein or ADAMTS-R1 protein or with a sequence contained within its corresponding antisense strand. Such hybridization probes bind to the sense strand under stringent conditions. The term "stringent conditions" as used herein is the binding which occurs 30 within a range from about Tin 5'C (5'C below the melting temperature

Tm of the probe) to about 20°C to 25°C below Tm. The probes are used in Northern assays to detect transcripts of ADAMTS-N homologous genes and in Southern assays to detect ADAMTS-N homologous genes. The identity of probes which are 200 nucleotides 5 in length and have 5 full complementarity with a portion of the antisense strand of a double-stranded DNA molecule which encodes the ADAMTS-N protein is determined using the nucleotide sequences shown in FIG 1 - 10 and described by the general formula a-b; where a is any integer between I and the position number of the nucleotide which is located 200 .

10 residues upstream of the 3' end of the sense or antisense strand of the cDNA sequences shown in FIG 1 -10; b is equal to a +200; and where both a and b correspond to the positions of nucleotide residues of the cDNA sequences shown in FIG 1-10.

Such probes or primers are also useful for identifying tissues 15 or cells in which the corresponding ADAMTS-N or ADAMTS-R1 gene is preferentially expressed either constitutively or at particular state of tissue differentiation or development or in disease states. Expression of the ADAMTS-N or ADAMTS-R1 gene in a particular tissue or group of cells is determined using conventional procedures 20 including, but not limited to, Northern analysis, in situ hybridization to RNA or RT-PCR amplification. Isolated polynucleotides encoding an ADAMTS-N or ADAMTS-R1 protein are also useful as chromosome markers to map linked gene positions, to identify chromosomal aberrations such as translocations, inversions 25 and trisomies, to compare with endogenous DNA sequences in patients to identify potential genetic disorders, and as probes to hybridize and thus discover novel, related DNA sequences. For use in such studies and assays, the probes may be labeled with radioisotopes, fluorescent labels, or enzymatic labels. The assays include, but are 30 not limited to, Southern blot, in situ hybridization to DNA in cells

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and chromosomes, PCR, and allele specific hybridization.

Antibodies

In another aspect, the present invention relates to antibodies which are specific for and bind to the ADAMTS-5 protein, the ADAMTS-6 5 protein, the ADAMTS-7 protein, the ADAMTS-8 protein, the ADAMTS-9 protein, the ADAMTS-10 protein, or the ADAMTS-R1 protein. Such antibodies are useful research tools for identifying *tissues that contain elevated levels of the respective protein and for purifying the respective protein from cell or tissue extracts, medium of 10 cultured cells, or partially purified preparations of intracellular and extracellular proteins by affinity chromatography. Such antibodies are also useful for identifying and diagnosing diseases associated with elevated or reduced levels of an ADAMTS-N protein or ADAMTS-R1 protein. Such antibodies are also useful for monitoring 15 the effect of therapeutic agents on the synthesis and secretion of ADAMTS-N proteins by cells in vitro and in vivo. Such antibodies may also be employed in procedures, such as co-immunoprecipitation and co-affinity chromatography, for identifying other proteins, activators and inhibitors which bind to an ADAMTS-N or ADAMTS-R1 20 protein.

The present invention also provides a method for detecting an ADAMTS-N or ADAMTS-R1 protein, in a bodily sample from a patient using antibodies immunospecific for an ADAMTS-N or ADAMTS-R1 protein. The method comprises contacting the antibody with a sample taken from 25 the patient; and assaying for the formation of a complex between the antibody and the corresponding ADAMTS-N or ADAMTS-R1 protein present in the sample. The sample may be a tissue or a biological fluid, including but not limited to whole blood, serum, synovial fluid, stool, urine, cerebrospinal fluid, semen, diagnostic washes from 30 trachea, stomach and other bowel segments, tissue biopsies or excised

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tissue, cells obtained from swabs and smears. To monitor changes in expression of the ADAMTS-N protein during fetal development and pregnancy, it is preferred that the sample be amniotic fluid. To monitor changes in expression of the ADAMTS-N protein during joint 5 disorders, the preferred sample is synovial fluid. To monitor changes in expression of ADAMTS-N proteins during cancer, the preferred samples include, but are not limited to, serum, body fluids, or biopsy tissue. To monitor changes in expression of ADAMTS-N proteins during inflammation the preferred samples include, to but are not limited to, serum, body fluids, or biopsy tissue.

The sample may be untreated, or subjected to precipitation; fractionation, separation, or purification before combining with the anti-ADAMTS-N protein antibody. For ease of detection, it is

preferred that isolated proteins from the sample be attached to

15 a substrate such as. a column, plastic dish, matrix, or membrane,

preferably nitrocellulose. Preferably, the detection method employs

an enzyme-linked immunosorbent assay (ELISA) or a Western immunoblot

procedure.

Interactions between an ADAMTS-N protein in the sample and the corresponding anti ADAMTS-N antibody are detected by radiometric, colorimetric, or fluorometric means, size separation, or precipitation. Preferably, detection of the antibody-ADAMTS-N protein complex is by addition of a secondary antibody that is coupled to a detectable tag, such as for example, an enzyme, 25 fluorophore, or chromophore. Formation of the complex is indicative of the presence of the ADAMTS-N protein in the test sample. Thus, the method is used to determine whether there is a decrease or increase in the levels of the ADAMTS-N protein in a test sample as compared to levels of the ADAMTS-N protein in a control sample and to 30 quantify the amount of the ADAMTS-N protein in the test sample.

Deviation between control and test values establishes the parameters for diagnosing the disease.

Preparing the ADAMTS-N proteins and the ADAMTS-R1 protein

The ADAMTS-N proteins and the ADAMT-SR1 protein may be produced 5 by conventional peptide synthesizers. The ADAMTS-N proteins and the ADAMTS-R1 protein may also be produced using cell-free translationsystems and RNA molecules derived from DNA constructs that encode an ADAMTS-N protein or an ADAMTS-RI protein. Alternatively, ADAMTS-N proteins are made by transfecting host cells with expression 10 vectors that comprise a DNA sequence that encodes the respective ADAMTS-N protein and then inducing expression of the protein in the host. cells. For recombinant production, recombinant constructs comprising one or more of the sequences which encode the ADAMTS-N protein or a variant thereof are introduced into host cells by 15 conventional methods such as calcium phosphate transfection, DEAE-dextran mediated transfection, transvection, microinjection, cationic lipid-mediated transfection, electroporation, transduction, scrape lading, ballistic introduction or infection.

The ADAMTS-N protein and the ADAMTS-R1 protein may be expressed 20 in suitable host cells, such as for example, mammalian cells, yeast, bacteria, insect cells or other cells under the control of appropriate promoters using conventional techniques. Suitable hosts include, but are not limited to, E. coli, P. pastoris, Cos cells and 293 HEK cells. Following transformation of the suitable host strain 25 and growth of the host strain to an appropriate cell density, the cells are harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification of the ADAMTS-N protein or the ADAMTS-R1 protein.

Conventional procedures for isolating recombinant proteins from 30 transformed host cells, such as isolation by initial extraction from

cell pellets or from cell culture medium, followed by salting-out, and one or more chromatography steps, including aqueous ion exchange chromatography, size exclusion chromatography steps, and high performance liquid chromatography (HPLC), and affinity chromatography may be used to isolate the recombinant ADAMTS-N protein or ADAMTS R1 protein

Preparation of Antibodies

The ADAMTS-N proteins, and variants thereof are used as immunogens to produce antibodies immunospecific for one or more

10 ADAMTS-N protein. The term "immunospecific" means the antibodies have substantially greater affinity for one or more ADAMTS-N protein than for other proteins. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, and Fab fragments.

- Antibodies are also prepared using an oligopeptide having a sequence which is identical to a portion of the amino acid sequence of an ADAMTS-N protein. Preferably the oligopeptide has an amino acid sequence of at least five amino acids, and more preferably, at least 10 amino acids that are identical to a portion of the amino
- 20 acid sequence of an ADAMTS-N protein. Such peptides are conventionally fused with those of another protein such as keyhole limpet hemocyanin and antibody produced against the chimeric molecule. One preferred oligopeptide for preparing an antibody to mouse ADAMTS-5 has the sequence (C)HIKVRQFKAKDQTRF, SEQ ID NO: 30.
- 25 Another preferred oligopeptide for preparing an antibody to ADAMTS-5 is CEAKNGYQSDAKGVKTFVEWVPKYAG, SEQ ID NO: 3 1. One preferred oligopeptide for preparing an antibody to ADAMTS-6 has the sequence SVSIERFVETLVVADK(C), SEQ ID NO:23. One preferred oligopeptide for preparing an antibody to ADAMTS-7 has the sequence
- 30 (C) EVAEAANFLALRSEDPEKY, SEQ ID NO:24. One preferred oligopeptide for

preparing an antibody to ADAMTS-8 has the sequence

CVKEDVENPKAVVDGDWGP, SEQ ID NO:25. One preferred oligopeptide for

preparing an antibody to ADAMTS-9 has the sequence

QHPFQNEDYRPRSASPSRTH, SEQ ID NO:26. Another preferred oligopeptide

for preparing an antibody to ADAMTS-9 has the sequence

PQNCKEVKRLKGASEDGEYF, SEQ ID NO:27. One preferred oligopeptide for

preparing an antibody for ADAMTS-R1 has the sequence QELEEGAAVSEEPS,

SEQ ID NO:28. Another preferred oligopeptide for preparing an

antibody for ADAMTS-R1 has the sequence YYPENIKPKPKLQE; SEQ ID NO:29.

10 Polyclonal antibodies are generated using conventional techniques by administering the ADAMTS-N protein or achimeric molecule to a host animal. Depending on the host species, various adjuvants may be used to increase immunological response. Among adjuvants used in humans, Bacilli Calmette-Guerin (BCG), and
15 Corynebacterium parvum. are especially preferable. Conventional protocols are also used to collect blood from the immunized animals and to isolate the serum and or the IgG fraction from the blood.

For preparation of monoclonal antibodies, conventional hybridoma techniques are used. Such antibodies are produced by 20 continuous cell lines in culture. Suitable techniques for preparing monoclonal antibodies include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV hybridoma technique.

Various immunoassays may be used for screening to identify
25 antibodies having the desired specificity. These include protocols
which. involve competitive binding or immunoradiometric assays and
typically involve the measurement of complex formation between the
respective ADAMTS-N protein and the antibody.

Polynucleotides that encode ADAMTS-N proteins

30 Polynucleotides comprising sequences encoding an ADAMTS-N

protein or an ADAMTS-R1 protein may be synthesized in whole or in part using chemical methods. Polynucleotides which encode an ADAMTS-N protein, particularly alleles of the genes which encode the ADAMTS-N protein, may be obtained by screening a genomic library or CDNA library with a probe comprising sequences identical or complementary to the sequences shown in Figures 1 - 10 or with antibodies immunospecific for a ADAMTS-N protein to identify clones containing such polynucleotide.

Example 1 ADAMTS-512 protein A cDNA encoding mouse ADAMTS-5 protein was obtained using IMAGE Clone 569515, purchased from Research Genetics, Huntsville, Alabama and 7 day old mouse embryo cDNA library from Clontech, Palo Alto, CA. A cDNA encoding human ADAMTS-5 protein was obtained using IMAGE Clone 345484 purchased from Research Genetics, Huntsville, Alabama 15 and a human fetal brain cDNA from Clontech. The clone inserts were sequenced in their entirety. Using oligonucleotide primers based on the sequences at the ends of the. clone inserts as template, successive rounds of RACE (Rapid Amplification of cDNA Ends) by PCR was performed at 5' and 3 ends. RACE primers were generated 50-200 20 bp from the ends of the sequences so that the contiguity of RACE clones with the I.M.A.G.E. clone could be clearly established. A single round of 5' and 3' 20 RACE sufficed for cloning of the entire coding sequence of the mouse ADAMTS-5 protein and part of the catalytic zinc binding site through to the stop codon of the human 25 ADAMTS-5 protein. Primers were designed with calculated Tm>72°C and RACE was performed with nested primers for each amplification. PCR used the Advantage PCR reagents (Clontech, Palo Alto, CA); the polymerase mix contained both Taq polymerase as well as proofreading polymerase to minimize PCR errors and employed "hot-start" PCR for 30 optimal efficiency. RACE used the following "touch-down" cycle

conditions; 95°C for 1 minute followed by 5 cycles of 95°C for 0.5
minutes, 72°C for 5 minutes, then 5 cycles of 95°C for 0.5 minutes,
70°C for 5 minutes and 20 cycles of 95°C for 0.5 minutes, 68°C for 5
minutes. The PCR products were analyzed by Southern blotting,
5 initially using [α³²P]-dCTP labeled.

Hybridizing bands were ligated into pGEM-T Easy (Promega, Madison, WI) and individual clones were selected by another round of Southern analysis. Automated nucleotide sequencing of both strands of each clone were done at the Molecular Biotechnology Core of the 10 Lerner Research Institute, Cleveland Clinic Foundation and nucleotide sequence data were analyzed using the DNAStar software. By integration of the overlapping sequences thus obtained, a contiguous nucleotide sequence was determined. The nucleotide sequence of the mouse ADAMTS-5 cDNA and the predicted amino acid sequence of the 15 protein encoded by this cDNA are shown in Fig. 1. The nucleotide sequence of the human ADAMTS-5 cDNA and the predicted partial amino acid sequence of the protein encoded by this cDNA are shown in Fig. 2.

The predicted molecular mass (Mr) of the mature ADAMTS-5

20 protein is 73717.50 daltons. It is expected that the actual Mr of the active ADAMTS-5 protein is different due to post-translational modification, which could potentially increase the Mr. The predicted domain organization of ADAMTS-5 protein relative to the cloned cDNA is shown in Figure 12. The pro-domain of the full-length mouse

25 ADAMTS-5 protein has 3 consensus cleavage signals for furin. The most carboxyl-terminal furin cleavage site in ADAMTS-5 predicts the processing site for generation of the mature protein The catalytic domain of the ADAMTS-5 protein contains eight cysteine residues and a reprolysin -zinc binding signature sequence, i.e., HEIGHLLGLSHD.

30 Five cysteine residues are upstream of the zinc binding sequence,

while three residues are downstream, an arrangement that is shared with other ADAMTS members. The zinc binding signature is followed by a "Met-turn". The catalytic domain is followed by a domain with 35% similarity to snake venom disintegrins. The disintegrin domain 5 contains eight cysteine residues. The first TS repeat contains 52 residues and is followed by a conserved cysteine-rich sequence termed the cysteine-rich domain, designated "CRD", to distinguish it from the cysteine-free spacer domain. The CRD contains ten conserved cysteines and demonstrates high sequence homology with the CRD of 10 other ADAMTS-N proteins. The spacer domain of mouse ADAMTS-5 is 158 amino acids in length and is followed by a second TS module. ADAMTS-5 contains three potential glycosylation sites in the mature protease one of which is just upstream of the start of the spacer domain and the second lies within the spacer domain and the third is near the 15 start of the disintegrin domain. The human ADAMTS-5 protein and the mouse ADAMTS-5 protein have 96% sequence identity. ADAMTS-5 bears 46% sequence identity to ADAMTS-4 (KIAA0688), which is characterized as being involved in catabolism of aggrecan core protein in arthritis and 60% identity to ADAMTS-1 which is involved in inflammation.

20 Example 2 ADAMTS-6

The nucleotide sequence of a human cDNA encoding the fulllength ADAMTS-6 protein was obtained using IMAGE clone 742630, which
encodes EST AA400393, and a human fetal brain cDNA from Clontech.
RACE was performed as described above in Example 1. The I.M.A.G.E.

25 clone 742630 contained an ORF flanked by consensus splice sequences,
indicating the presence of introns. Two successive rounds of RACE at
the 5' end and a single round of RACE at the 3' end provided the
complete coding sequence of ADAMTS-6. The putative ATG codon is
within a Kozak consensus sequence and encodes the first methionine
30 within the ORF.

3. 3

The nucleotide sequence of the ADAMTS-6 DNA is shown in Fig. 3 The predicted amino acid sequence, SEQ ID NO:6, of the ADAMTS-6 protein is also shown in Fig. 3. The predicted Mr of the fulllength, unprocessed ADAMTS-6 protein is 97,115 daltons., and the 5 predicted Mr of the mature ADAMTS-6 protein is 68412.10 daltons. domain organization of the ADAMTS-6 protein is shown in Fig. 12. pro-domain of the full-length ADAMTS-6 protein has one consensus cleavage signal for furin. The catalytic domain of the ADAMTS-6 contains six cysteine residues and the reprolysin -zinc binding 10 signature sequence, HEIVHNFGMNHD, which is followed by a "Met-tum". The catalytic domain is followed by a domain with 35% similarity to disintegrins. The disintegrin domain contains snake venom eight cysteine residues. The first TS repeat contains 52 residues and is followed by a conserve CRD sequence which contains ten 15 conserved cysteines and demonstrates high sequence homology with the CRD of other ADAMTS proteins. The spacer domain of ADAMTS-6 is 127 amino acids in length and is followed by a second TS module. ADAMTS-6 contains four potential glycosylation sites within the pyo-domain and two in the mature protease one of which is in the cysteine rich 20 domain and the other of which is in the spacer domain. ADAMTS-6 bears 46% sequence identity to ADAMTS-1, which is involved in inflammation.

Example 3 ADAMTS-7.

The nucleotide sequence of a cDNA encoding an ADAMTS-7 protein

25 was obtained using IMAGE clone 272098, which encodes EST N4.8032, and
a human fetal brain cDNA from Clontech. RACE was performed as
described above in Example 1. The I.M.A.G.E. clone 272098 encoded a
putative pre-pro region and was extended in the 3'-direction by two
successive rounds of RACE. A typical signal peptide sequence lies

30 downstream of the first methionine in the translated ORF. This

methionine codon lies within a satisfactory Kozak consensus for translation initiation.

The nucleotide sequence of the ADAMTS-7 cDNA is shown in Fig. 4. The predicted amino acid sequence, SEQ ID NO: 8, of the ADAMTS-7 5 protein is also shown in Fig. 4. The predicted Mr of the hilllength, unprocessed ADAMTS-7 protein is 116,607 daltons, and the predicted Mr of the mature ADAMTS-7 protein is 84005 daltons. The domain organization of the ADAMTS-7 protein is shown in Fig. 12. The pro-domain of the full-length ADAMTS-7 protein has one consensus 10 cleavage signal for furin. The catalytic domain of the ADAMTS-7 protein contains eight cysteine residues and the reprolysin-zinc binding signature sequence, HELGHSFGIQHD, which is followed by a "Met-tum". The catalytic domain is followed by a domain with 30% similarity to snake venom disintegrins The disintegrin domain 15 contains eight cysteine residues. The first TS repeat contains 52 residues and is followed by a conserved CRD sequence which contains ten conserved cysteines. The spacer domain of ADAMTS-7 is 221 amino acids in length and is followed by a second TS module and a short sequence containing two cysteine residues. ADAMTS-7 contains three 20 potential glycosylation sites within the mature protease; one of which is just upstream of the spacer domain and one of which is within the spacer domain. ADAMTS-7 bears 35 % sequence identity to

Example 4: ADAMTS-8

25 enzyme.

The nucleotide sequence of a cDNA encoding a full-length, mouse ADAMTS-8 protein was obtained using IMAGE clone 1260693, which encodes EST AA855532, and a mouse embryo cDNA from Clonetech. The 30 nucleotide sequence of a cDNA encoding a partial ADAMTS-8 human

ADAMTS-1, which is characterized as being involved in inflammation

and 32% identity to ADAMTS-2 which is a procollagen processing

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protein was obtained using IMAGE clone 2119838, which encodes EST A1400905, and a human fetal brain cDNA library from Clontech. RACE was performed, as described above in Example 1. The nucleotide sequence of the cDNA encoding the full-length ADAMTS-8 mouse protein and the amino acid sequence of such protein is shown in Fig. 5. The nucleotide sequence of the cDNA encoding the partial ADAMTS-8 human protein and the amino acid sequence of such protein is shown in Fig. 6.

The predicted Mr of the full-length, unprocessed ADAMTS-8 mouse 10 protein is 1260693 daltons, and the predicted Mr of the mature ADAMTS-8 protein is 68412.10 daltons. The pro domain of the fulllength ADAMTS-8 protein has one consensus cleavage signal for furin. The catalytic domain contains eight cysteine residues and the reprolysm-zinc binding signature sequence, HELGHVLSMPHD, which is 15 followed by a "Met-turn". The catalytic domain is followed by a domain with 20-30% similarity to snake venom disintegrins. The disintegrin-like domain contains eight cysteine residues. The first TS repeat is followed by a conserved CRD sequence which contains 10 conserved cysteines. The spacer domain of ADAMTS-8 is 146 amino 20 acids in length and is followed by a second TS module. The ADAMTS-8 protein contains 4 potential glycosylation sites within the mature protease: one is in the cysteine-rich domain; one is in the catalytic domain; and two are in the disintegrin-like domain. ADAMTS-8 bears 46% sequence identity to ADAMTS-1 and 42% identity to 25 ADAMTS-4.

Example 5: ADAMTS-9

The nucleotide sequence of a cDNA encoding a full-length, human ADAMTS-9 protein was obtained using IMAGE clone 646675, which encodes EST AA205581, and a human fetal brain cDNA from Clonetech. The 30 micleotide sequence of a cDNA encoding a partial ADAMTS-9 mouse

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protein was obtained using IMAGE clone 535663, which encodes EST AAl 06215, and a mouse cDNA library obtained from Clonetech. RACE was performed as described above in Example 1. The nucleotide sequence of the cDNA encoding the full-length ADAMTS-9 human proteinand the amino acid sequence of such protein is shown in Fig.6. The nucleotide sequence of the cDNA encoding the partial ADAMTS-9 mouse protein and the amino acid sequence of such protein is shown in Fig. 7.

The predicted Mr of the mature human ADAMTS-9 protein is

10 189777.20 daltons. The prodomain of the predicted ADAMTS-9 protein
has 3 consensus cleavage signal for furin. The catalytic domain of
the ADAMTS-9 contains eight cysteine residues and the reprolysin zinc binding signature sequence, HELGHVFNMPHD, which is followed by a
"Met-turn". The catalytic domain is followed by a domain with 25-30%
15 similarity to snake venom disintegrins The disintegrin domain
contains eight cysteine residues. The first TS repeat contains is
followed by a conserved CRD sequence which. contains 10 conserved
cysteines. The spacer domain of ADAMTS-9 is 124 amino acids in
length and is followed by 14 additional TS modules and a C-terminal
20 domain. The ADAMTS-9 protein contains 6 potential glycosylation
sites within the mature protease: one in the spacer domain, one in
TSP 1 -7, one in TSPI-8, and 3 in the C-terminal domain. The ADAMTS9 bears 44% sequence identity to ADAMTS-4.

Example 6: ADAMTS-10

The nucleotide sequence of a cDNA encoding a fall-length

ADAMTS- 10 protein was obtained using IMAGE clone 110403, which

encodes EST AA588434, and a human fetal brain cDNA from Clonetech.

The nucleotide sequence of a cDNA encoding a partial, mouse ADAMTS-10

protein was obtained using IMAGE clone 1077653, which encodes EST

30 AA822090, and a mouse embryo cDNA library from Clonetech. RACE was

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performed as described above in Example 1. The nucleotide sequence of the human ADAMTS-10 cDNA and the predicted amino acid sequence, SEQ ID 18, of the human ADAMTS-10 protein encoded by such DNA is shown in Fig. 9. The nucleotide sequence of the cDNA encoding the partial mouse ADAMTS-10 protein and the amino acid sequence of such protein is shown in Fig. 10.

The predicted Mr of the mature ADAMTS-10 protein is 95238 daltons. The pro-domain of the full-length ADAMTS-10 protein has no consensus cleavage signal for furin. The catalytic domain of the , 10 ADAMTS-10 contains eight cysteine residues and the reprolysin-zinc binding signature sequence, HEIGHTFGMNHD, which is followed by a "Met-turn". The catalytic domain is followed by a domain with 30% similarity to snake venom disintegrins. The disintegrin-like domain contains eight cysteine residues. The first TS repeat is followed by 15 a conserved CRD sequence which contains 8 conserved cysteines. The spacer domain of ADAMTS-10 is followed by 4 additional TS modules and a Kunitz domain. The ADAMTS-10 protein contains 2 potential glycosylation sites within the mature protease: one in the catalytic domain, and one in the TS 1-3 domain. ADAMTS-10 bears approximately 40% sequence identity to ADAM-TS1, which is characterized as being involved in inflammation.

Comparison of the ADAMTS-N Proteins.

As shown in Figure 11, the ADAMTS-5. ADAMTS-6, and ADAMTS-7 proteins share a common domain organization. From amino to carboxyl 25 termini, they are as follows:

1. A pre-pro region. A typical signal sequence of variable length is followed by a putative pro-region of variable length but demonstrating short stretches of sequence identity. Three cysteine residues are, predicted within each novel pro-domain, of which the
30 most C-terminal is an "asymmetric" cysteine lying within a sequence

context similar to the cysteine "switch" of the MMPs. All three novel cDNAs predict consensus cleavage signals for furin, three in the case of ADAMTS-5, and one each in the case of ADAMTS-6 and ADAMTS-7. The most carboxyl-terminal furin cleavage site in ADAMTS-5 predicts the processing site for generation of the mature protease. The amino terminus of the mature proteins is predicted to start at the residue immediately following the cleavage sites.

- 2. A catalytic domain. The catalytic domains are very similar to each other and contain eight cysteine residues and a typical
- 10 reprolysin-type zinc binding signature followed by a "Met-turn".

 Five cysteine residues are upstream of the zinc binding sequence,
 while three residues are downstream, an arrangement that is shared
 with other ADAMTS members. The methionine of the met-turn is not at
 a constant distance from the zinc-binding signature, but in all three
 15 novel proteases, a constant cysteine residue is present in that
 interval.
- 3. A disintegrin-like domain. The catalytic domain is followed by a domain of 60-90 residues with 35-45% similarity to snake venom disintegrins, but without the canonical cysteine arrangement seen in the latter. This disintegrin-like domain is of comparable length in ADAMTS-5 and ADAMTS-7, it is considerably shorter in ADAMTS-6.
- 4. A TS module. The first TS repeat is very similar in all three novel proteases and very similar to the first TS repeat of other ADAMTSs. It contains the same number of residues (fifty-two) in all 25 three novel proteins.
 - 5. The cysteine-rich domain. This TS domain is followed by a conserved cysteine-rich sequence termed the cysteine-rich domain (CRD).
- 6. The spacer domain. This domain is of variable length, in all 30 ADAMTSs and lacks the sequence landmarks so characteristic of all the

other domains. It shows the least homology of all the domains.

7. A C-terminal TS module. The sequence of the second TS module is more variant between the members of the ADAMTS family than the first TS module, despite the conservation of the number and spacing 5 of cysteine residues.

Overall, the predicted mature forms of these proteases show 20-30% similarity to each other and to ADAMTS1-4 although this may be considerably higher or lower for individual domains as described above.

- ADAMTS-9 and ADAM-TS10 contain all the domains present in ADAMTS-5 through ADAMTS-8. In addition, ADAMTS-9 and ADAMTS-10 contain the following domains:
- A. ADAMTS-9: After the c-terminal TS1 domain which is present in ADAMTS5-8, ADAMTS-9 contains 13 additional and homologous 15 TS11 domains, thus, ADAMTS-9 contains a total of 15 TS1 domains, of which 14 are adjacent to each other in the c-terminal half of the molecule. The 15th TS1 domain from the N-terminus is followed by a unique c-terminal domain which does not possess recognizable domain structure and contains 196 residues including 9 cysteine residues.
- B. ADAMTS-10: After the c-terminal TS1 domain which is present in ADAMTS 8, ADAMTS-10 contains 3 additional and homologous TS1 domains, thus, that ADAMTS-10 contains a total of 5 TS1 domains, of which 4 are adjacent to each other in the c-terminal half of the molecule. The 5th TS 1 domain from the N-terminus is followed by an 25 additional 47 amino acid residues including six (6) cysteine
- residues. These 47 residues have sequence similarity of 30%-40% to the c-terminus of pro-hormone convertase 5 and 6, and to the Kunitz family of inhibitors.

Northern Analysis

Mouse embryo northern blots and multiple tissue northern blots

from human and mouse tissues (Clontech, Palo Alto, CA) were hybridized to the $[\alpha^{32}P]$ -dCTP labeled inserts of I.M.A.G.E. clones as per the manufacturer's recommendations followed by autoradiographic exposure for 3-7 days.

In situ hybridization used cryosections of mouse embryos of gestational age 8.5 days and 10.5 days. Embryos were collected with the inclusion of the surrounding uterus and fixed overnight in 4% paraformaldehyde. Sense and anti-sense probes continuously labeled with digoxigenin-UTP (Boehringer-Mannheim, Indianapolis, IN) were 10 transcribed with T7 and T3 RNA polymerases, respectively, using as template a 63 0 bp EcoRI-Sacl fragment from the Adamts-5 clone 569515 (Fig. 14) cloned into pBluescript SK+ (Stratagene, La Jolla, CA). In situ hybridization was done essentially as previously described in Apte, et al. (1997) J. Biol. Chem. 272:2551-25517, which is 15 specifically incorporated herein by reference, except that sections were predigested with proteinase K (Boehringer-Mannheim, Indianapolis, IN) at a lower, concentration (1 -5 μ g/ml) than reported in Apte, et al.. Bound, digoxigenin-labeled probe was detected using an alkaline phosphatase tagged anti-digoxigenin 20 antibody (Boehringer-Mannheim, Indianapolis, IN) and nuclei were counterstained with methyl green.

Specific hybridization of the antisense Adamts-5 probe to sections of 8.5 day-old mouse embryos was obtained, whereas only low background staining was noted with the control sense probe. Staining 25 was uniform throughout the 8.5 day old embryos. In addition, there was labeling of mRNA in trophoblastic cells lining the uterine cavity as well as in the developing placenta (Fig. 14). The decidual reaction within the uterus also showed upregulation of Adamts-5 mRNA relative to the negative controls. In sections from 10.5 day old 30 embryos, labeling was widespread but less intense compared to the 8.5

day-old embryo. Labeled cells were seen in mesenchyme and somites as well as in the neural tube and developing hindgut. Northern analysis also indicated that mRNA encoding ADAMTS-5 was present in human placenta but was barely detectable in adult lung, heart, brain, 5 liver, skeletal muscle, kidney and pancreas.

Northern analysis showed undetectable expression of Adamts-6 during mouse embryo development. Northern analysis indicated that mRNA encoding ADAMTS-6 was present in human placenta but was barely detectable in adult lung, heart, brain, liver, skeletal 10 muscle, kidney and pancreas. Adamts-7 was expressed at low levels throughout mouse development. In adult human tissues examined with human cDNA probes, ADAMTS-7 mRNA was found in all tissues examined, i.e. in lung, heart, brain, liver, skeletal muscle, kidney, pancreas and placenta. The sizes of the mRNA species recognized by the probes 15 varied. ADAMTS-5 mRNA was approximately 10 kbp in size in human tissue. The most prominent Adamts-5 species was estimated at 7.5 kbp together with additional bands at 10 kbp and 4.5 kbp. The lone mRNA species detected by ADAMTS-6 probe was approximately 8.5 kbp, whereas the most common mRNA species detected by ADAMTS-7 probe 5 was 5 kbp 20 in size with an additional species seen at 7 kbp in skeletal muscle.

In mouse, ADAMTS-8 is expressed during fetal development (days 7, 11, 15, 17) and in adult mouse lung and heart with an mRNA size of approximately 3.8 kbp. In adult human tissue, ADAMTS-8 is expressed in lung and brain but not in heart, muscle, kidney, colon or thymus.

25 The mRNA size is 3.8 kbp.

ADAMTS-9 is expressed in lung, ovary placenta, heart, brain, muscle, kidney and pancreas with a mRNA size of 8 kb. In addition, kidney and ovary contain additional transcripts of size 3 kb and 4.4 kb respectively. These additional transcripts may represent 30 alternatively spliced or short forms of ADAMTS9.

ADAMTS-10 is expressed in thymus, prostate, testis, ovary, small intestine, colon, peripheral blood leukocytes, heart, brain, placenta, lung, liver, muscle, kidney and pancreas, as well as in many cell lines such as A549, HeLa and K562. There are two 5 transcripts of 5 kb and 8kb present in all tissues.

Example 7: ADAMTS-R1

The nucleotide sequence of a cDNA encoding a full-length ADAMTS-R1 protein was obtained using IMAGE clone 752797 which encodes EST AA, and a human fetal brain cDNA from Clontech. RACE was 10 performed as described above in Example 1. The nucleotide sequence, SEQ ID NO:21, of the ADAMTS-R1 cDNA and the predicted amino acid sequence, SEQ ID NO:22, of the ADAMTS-R1 protein encoded by such DNA is shown in Fig. 11.

The predicted Mr of the full-length, unprocessed ADAMTS-R1 15 protein is 58358.20 daltons. The domain organization of the ADAMTS-10 protein is shown in Fig. 15. In contrast to the ADAMTS-N proteins of examples 1-6, ADAMTS-R1 protein does not have a prometalloprotease or disintegrin-like domain or a consensus cleavage signal for furin. ADAMTS-R1 has a signal (pre) peptide which is 20 followed by a first TS module and a conserved CRD sequence which contains 10 conserved cysteines. The spacer domain of ADAMTS-R1 is 115 amino acids in length and is followed by 3 additional TS modules and a short sequence of 33 amino acids. The ADAMTS-R1 protein contains one potential glycosylation sites which is in the spacer 25 domain. ADAMTS-R1 bears 30-40% sequence identity to ADAMTS1 and ADAMTS4 in the related domains. ADAMTS-R1 mRNA is present in human heart, brain, kidney, muscle, lung, placenta, testis, ovary, colon, intestine, and prostate. There are three transcripts of 2.5 kb, 4.7 kb and 6.5 kbp present in all such tissues. In mouse, expression is 30 seen in skeletal muscle, and the transcript size is 6.5 kb.

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Although certain embodiments of this invention have been shown and described, various adaptations and modifications can be made without departing from the scope of the invention as defined in the appended claims.

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CLAIMS

- 1. An isolated mammalian protein selected from the group consisting of an ADAMTS-5 protein an ADAMTS-6 protein, an ADAMTS-7 protein, an ADAMTS-8 protein, an ADAMTS-9 protein, an ADAMTS-10 protein, and an ADAMTS-R1 protein.
- The isolated mammalian protein of claim 1 wherein said protein 2. comprises an amino acid sequence which is at least 95% identical to a sequence selected from the group consisting of: amino acid 262 through amino acid 930 of SEQ ID NO:2; amino , acid 1 through amino acid 518 of SEQ ID NO:4; amino acid 245 10 through amino acid 860 of SEQ ID NO:6; amino acid 233 through amino acid 997 of SEQ ID NO:8; amino acid 229 through amino acid 905 of SEQ ID NO:10; amino acid 1 through amino acid 245 of SEQ ID NO:12; amino acid 236 through amino acid 1882 of SEQ ID NO:14; amino acid 1 through amino acid 874 of SEQ ID NO:16; 15 amino acid 212 through amino acid 1081 of SEQ ID NO:18; amino acid 1 through amino acid 450 of SEQ ID NO:20; and amino acid 1 through amino acid 547 of SEQ ID NO:22.
- The isolated protein of claim 2 wherein said amino acid
 sequence further comprises a prepropeptide sequence at the amino terminus thereof.
 - 4. The isolated protein of claim 1 wherein said protein is a human ADAMTS-5 protein or a mouse ADAMTS-5 protein.
- 5. The isolated protein of claim 1 wherein said protein is a human25 ADAMTS-6 protein.
 - 6. The isolated protein of claim 1 wherein said protein is a human ADAMTS-7 protein.
 - 7. The isolated protein of claim 1 wherein said protein is a mouse ADAMTS-8 or a human ADAMTS-8 protein.
- 30 8. The isolated protein of claim 1 wherein said protein is a human

- ADAMTS-9 or a mouse ADAMTS-9 protein.
- 9. The isolated protein of claim 1 wherein said protein is a human ADAMTS-10 or a mouse ADAMTS-10 protein.
- 10. The isolated protein of claim 1 wherein said protein is a human ADAMTS-R1 protein.
- 11. An isolated polynucleotide comprising a sequence which encodes a mammalian protein selected from the group consisting of an ADAMTS-5 protein, an ADAMTS-6 protein, an ADAMTS-7 protein, an ADAMTS-8 protein, an ADAMTS-9 protein, an ADAMTS-10 protein, and an ADAMTS-R1 protein.
- 12. The isolated polynucleotide of claim 11 wherein said protein comprises an amino acid sequence which is at least 95% identical to a sequence selected from the group consisting of: amino acid 262 through amino acid 930 of SEQ ID NO:2; amino 15 acid 1 through amino acid 518 of SEQ ID NO:4; amino acid 245 through amino acid 860 of SEQ ID NO:6; amino acid 233 through amino acid 997 of SEQ ID NO:8; amino acid 229 through amino acid 905 of SEQ ID NO:10; amino acid 1 through amino acid 245 of SEQ ID NO:12; amino acid 236 through amino acid 1882 of SEQ 20 ID NO:14; amino acid 1 through amino acid 874 of SEQ ID NO:16; amino acid 212 through amino acid 1081 of SEQ ID NO:18; amino acid 1 through amino acid 450 of SEQ ID NO:20, and amino acid 1 through amino acid 547 of SEQ ID NO:22.
- 13. The isolated polynucleotide of claim 11 wherein said nucleotide
 25 sequence encodes a protein having a signal sequence at the amino terminus thereof.
- 14. The isolated polynucleotide of claim 11 wherein said polynucleotide comprises a sequence selected from the group consisting of: nucleotide 800 through nucleotide 2810 of SEQ ID NO:1 of an allelic variant thereof; nucleotide 1 through

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nucleotide 1519 of SEQ ID NO:3 or an allelic variant thereof; nucleotide 754 through nucleotide 2602 of SEQ ID NO:5 or an allelic variant thereof; nucleotide 708 through nucleotide 3003 of SEQ ID NO:7 or an allelic variant thereof; nucleotide 962 through nucleotide 2992 of SEQ ID NO:9 or an allelic variant thereof; nucleotide 1 through nucleotide 739 of SEQ ID NO:11 or an allelic variant thereof; nucleotide 708 through nucleotide 5648 of SEQ ID NO:13 or an allelic variant thereof; nucleotide 1 through nucleotide 2625 of SEQ ID NO:15 or an allelic variant thereof; nucleotide 634 through nucleotide 3243 of SEQ ID NO:17 or an allelic variant thereof; nucleotide 1 through nucleotide 1642 of SEQ ID NO:19 or an allelic variant thereof; and nucleotide 51 through nucleotide 1625 of SEQ ID NO:21 or an allelic variant thereof.

- 15 15. The isolated polynucleotide of claim 11 wherein said polynucleotide hybridizes under stringent conditions to a nucleic acid molecule comprising a sequence complementary to the protein encoding sequence of SEQ ID NO:1; SEQ ID NO:3; SEQ ID NO:5; SEQ ID NO:7; SEQ ID NO:9; SEQ ID NO:11; SEQ ID NO:13; SEQ ID NO:15; SEQ ID NO:17; SEQ ID NO:19; or SEQ ID NO:21.
 - 16. An isolated polynucleotide having a sequence which is complementary to the protein encoding sequence of the polynucleotide of claim 11.
 - 17. An expression vector comprising a polynucleotide of claim 11.
- 25 18. A host cell transformed or transfected with an expression vector of claim 17.
 - 19. A method for producing an ADAMTS-N protein or an ADAMTS-R1 protein, said method comprising the steps of
- (a) culturing a host cell of claim 18 under conditions

 30 suitable for expression of an ADAMTS-N protein or an ADAMTS-R1

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protein; and

- (b) recovering said ADAMTS-N protein or said ADAMTS-R1 protein from the host cell culture.
- 20. An antibody that binds to a protein selected from the group consisting of an ADAMTS-5 protein, an ADAMTS-6 protein, an ADAMTS-7 protein, an ADAMTS-8 protein, an ADAMTS-9 protein, an ADAMTS-10 protein and an ADAMTS-R1 protein.
- 21. An oligopeptide for producing an antibody that binds to an ADAMTS-N protein or an ADAMTS-R1 protein wherein said
- oligopeptide has a sequence selected from the group consisting of:
 - a) SVSIERFVETLVVADK, SEQ ID NO:23;
 - b) EVAEAANFLALRSEDPDKY, SEQ ID NO:24;
 - c) VKEDVENPKAVVDGDWGP, SEQ ID NO:25;
- d) QHPFQNEDYRPRSASPSRTH, SEQ ID NO:26;
 - e) PQNCKEVKRLKGASEDGEYF, SEQ ID NO:27;
 - f) QELEEGAAVSEEPS, SEQ ID NO:28;
 - g) YYPENIKPKPKLQE; SEQ ID NO:29;
 - h) HIKVRQFKAKDQTRF; and
- 20 i) CEAKNGYQSDAKGVKTFVEWVPKYAG, SEQ ID NO:30.

Fig. 1

'MRLEWASLILILLLLSASCLSLAADSPAAAPAQDKTRQPQAAAA
AAEPDQPQGEETRERGHLQPLAGQRRSGLVHNIDQLYSGGKVGYLVYAGGRRFLLD
LERDDTVGAAGSIVTAGGGLSASSGHRGHCFYRGTVDGSPRSLAVFDLCGGLDGFFAV
KHARYTLKPLLRGSWAEYERIYGDGSSRILHVYNREGFSFEALPPRASCETPASPSGP
QESPSVHSRSRRRSALAPQLLDHSAFSPSGNAGPQTWWRRRRSISRARQVELLLVAD
SSMARMYGRGLQHYLLTLASIANRLYSHASIENHIRLAVVKVVLTDKDTSLEVSKNA
ATTLKNFCKWQHQHNQLGDDHEEHYDAAILFTREDLCGHHSCDTLGMADVGTICSPER
SCAVTEDDGLHAAFTVAHEIGHLLGLSHDDSKFCEENFGTTEDKRLMSSILTSIDASK
PWSKCTSATITEFLDDGHGNCLLDLPRKQILGPEELPGQTYDATQQCNLTFGPEYSVC
PGMDVCARLWCAVVRQGQMVCLTKKLPAVEGTPCGKGRVCLQGKCVDKTKKKYYSTSS
HGNWGSWGPWGQCSRSCGGGVQFAYRHCNNPAPRNSGRYCTGKRAIYRSCSVTPCPPN

Fig. 1 (con't)

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Fig. 2

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Fig. 3

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Fig. 3 (con't)

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Fig. 4

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Fig. 4 (con't)

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  3061 teteceteca ggggacacag etececeteg atagaccagt ccagtggece eteaceacac
  3121 tgacttattt ccctaaacta tttataaaaa gtagggcaat ttcattaact ctgactctta
  3181 cctgcccggg cggccgctcg agccgagtaa tcactagt
```

Fig. 5A

	10	20	30	40	50	60	70
بسلس	بلينيل	سلسسلس	سلسسلس	بليبيلب	بيلينيان	سلنسلب	<u></u>
tagggcgad	ctgcacgg	gacgccgcgga	aggacgcgcgc	tegeggeeeg	gggcgccacg	tgctcgagtt	ctg 70
ctaggttgg	gctggcgc	aggaggagcgc	gctgcgcgate	ccagaggggc	cgccagggac	cgccgcgcca	cgt 140
gccgctago	ccgagtcg	gcctccccato	cgattgatca	ttttcctgg	yacagagcgac	ccggccgcct	.cgg 210
gccaccago	cacctgcc	cgcgcgcggcg	gatettettee	ctctcccgcg	rctccgcagca	ctctgcccc	ATG 280
CICCGCGAC	CCCCACCA	CCACCGGGTGC	3CCGCCCCCICC	IGCIGCIGCI	ATTICCACCIG	caccacacac	CAC 350
	360	370	380	390	400	410 .	420
			سلسيلي				
TCGICIGO	3GAGCCCC	3603663333	CAACCCCCCCCC	3CAGGCCTCG	GAGCTAGTGG	TGCCCACGCC	GTT 420
GCCCGGCA(3CGCGAGO	GAGCICGCCIT	CCACCIGICO	300000000	AGGCTTCGT	CCICCCCCIC	GCG 490
CCTGACGC	CAGCTTCC	TGGCGCCGGAA	VITCAAGATCG	AGCGCCTCGC	EGGCTCGAGC	600000000	GGG 560
GCGAGCCG	3GACTGCG	TOGCTGCTTCT	TCTCTGGCAC	AGIGAATGGA	GAACGGGAGI	CCCIGCCGC	GAT 630
GAGCIGIG:	ICCCCCCCCC	TGGAGCGGCTC	GITCITGCIG	CAGGCGAGC	AGTTCACCAT	CCAGCCACAC	1990 700
•	710	720	730	740	750	760	770
سيلسب	عليتناء	بالبينايي	سلسسلت	بطبيبلي	سلسسلس	بالتنبلين	لب
			rcecciecaeo				
GCLCCCL	GCCGCCGA	AGTTTTCCCCC	CICCCTCAAGG	ACTOGAGTO(CACCICCACA	TOGGIAATO	GCA 840
GGGACAGG	AGAGAAGT	GACAACGAAG	AGGACAGGAAG	CAGGACAAG	:AGGGGTTGCT	CAAAGAGACA	GAA 910
GACICCCG	CAAAGIGC	CACCACCCTT	CCGATCCAAAA	CTAGAAGCA	AGAGGITIGIC	FICCGAGGCIC	GCT 980
TOGIOGAA	ACACTICI	GGIGGCIGAT	CGTCCATGGC	TGCCTTCTA	rgggaccgacc	TIGCAGAACC	ACAT 1050
1	L060	1070	1080	1090	1100	1110	1120
سيلنين	ىلىسىل	سسسس	سلسسلس	uluul	uluulu	uduul	
CCTCACGG	TGATGICA	ATGGCAGCCC	GAATCTACAAG	CACCCGAGC	ATCAGGAACIC	CCGICAACCI.	IGIG 1120
GIGGIGAA	AGIGCTAA	TAGTGGAAAA	AGAAAGATGGG	GCCCGGAAG	IGICCGACAAC	COCCCCCC	ACAC 1190
TGCGCAAC	TTCTGCAG	CIGGCAACGG	CGITICAACAA	GCCCAGTGA	CCGCCACCCC	EAGCACTATG	ACAC 1260
TGCCATCT	TGITCACC	'AGACAGAACT	TCTGTGGGAAG	GGAGAGCAG	TGTGACACCC	iGGGGAIGGC	AGAC 1330
GITGGCAC	CATCTGTG	ACCCCGACAA	GAGCIGCICAC	TGATCAAGG	ATGAGGGACT	CAGGCAGCC	FACA 1400
	1410	1420	1430	1440	1450	1460	1470
			ىبلىسىلىن				
			CICAGCAIGC				
			TGGCGCCATTC				
			CTCCTCCATC				
			.C1CCCGGGGCCX				
GCAGATCI	TIGGGCC	CATTTCCGAC	ACTGCCCCAAC	CACCICIGIG	GAGGACATCT	GIGICCAGCI	CIGT 1750

Fig. 5A (con't)

1760	1770	1780	1790	1800	1810	.1820
<u> ئىسلىسىلىسىل</u>						
GCCCGTCATCGCGATA	GTGATGAGCC	CATTIGCCAC	ACAAAGAATO	GIAGCCIGCI	CICCCCICAT	GGIA 1820
CACCCTGTGGCCCTGG						
GCTGTGGTAGATGGA						
ATACAATTCTCGAACC						
CAGTCAAGTACCAATC	ATGCAACACA	<i>LGAGGAATGTC</i>	CACCAAACG	AAAAAGCTIC	CGGGAGCAGC	AGTG 2100
2110	2120	2130	2140	2150	2160	2170
<u> سىلىسىلىسىل</u>	بلتستليب	بلينيلين	بلينيلين	بلينينليب	بليستلين	
TGAGAAATATAATGCC						
GCAGTGTCCCCCCGAG	ACCGATGCAA	CCIGITITICC	AGAGCCCCTC	CGAGGAGTGA	GITCAAAGIG	TTTG 2240
AAGCTAAGGTGATCGA						
TAAGGCTGGCTGTGAC						
CCCACTGCCTGTAGGA	AGATCTCCGG	TTCTTTCACO	CCCTTCAGTT	ATGGCTACAA	IGACATIGIC	ACCA 2450
2460	2470	2480	2490	2500	2510 [.]	2520
نلىسلسسلىس	بالمسلم	علىبتطنين	ىلىنىلىن	بلينينلين	طينطين	<u> </u>
TCCCAGCTGGTGCCAC	AAACATTGAT	CIGAAACACO	GGAGTCACCC	AGGGTTCAGG	AACGACGGCA(GCTA 2520
CCTGGCGCTGAAGACA	CCCAATCCCC	AGIACCICCI	CAATGGTAAC	CIGGCCAICI	CTGCCATAGA	GCAA 2590
GACATCTTGGTGAAGG	GGACCATCCI	GAAGTACAGT	GGCTCCATGG	CTACCCTGGA	GCGGCTGCAG	AGCT 2660
TCCAGGCCCTGCCTGA	GCCTCTTACA	GTACAGCTCC	TGACTGTGTC	TCCTCACCTC	TTCCCTCCAA	AAGT 2730
CAGATATACCTTCTTT	GICCCCAATG	ACATGGACTT	CAGCGIGCAG	AATAGCAAGG	AAAGAGCAAC	CACC 2800
2810	2820	2830	2840	2850	2860	2870
بيسيليسين	بلينيلين	سيسلس	uuluulu	بليتيايي	بليبيلين	
AACATCATTCAGTCAC	TGCCCTCTGC	CGAGTGGGTT	CTGGGAGACT	GGICIGAAIG	TCCGAGCACG	IGCA 2870
GAGGIAGCIGGCAGCG	GCGGACTGTG	CAATGCAGG	ACCCCTCAGG	TCAGGCCTCT	GACACCIGIG	ATGA 2940
GGCTCTGAAACCTGAG	GATGCCAAGC	CCTGTGGAAG	CCAGCCGIGI	CCCCTCtgat	ccccttggtg	gaaa 3010
tctcttaggcttatgg	atttg gg cta	ctggtgtaac	agacaaaggt	.cccctccaag	gtgatactac	atat 3080
caagatggcacggccc	tttcaggcct	tctattacta	caaccccttg	ggtactacct	aattcataag	gaag 3150
3160	3170	3180	3190	3200	3210	3220
<u> ئاسىلىسلىسلى</u>	بليينانين	بليستلين	بليستليب	بليستانين	بلينتلين	<u></u>
agagaagagggtataa	gggtaacaga	ittgtaaagtt	gactgtctgg	rtggactggac	cttgcttatg	acca 3220
agaagtcgggataggt						
tttgcaaaggactagc	aaagctaaat	gaaaaagaag	aattttttt	ttctatttgg	tttccccaat	aatc 3360
aatctacctcacagcg						
agcaagctccataggt	atctccaago	tatcitcaga.	aatgtccgtg	gctgttttca	gtattaaaat	ctgt 3500

Fig. 5A (con't)

	3510	3520	3530	3540	3550	3560	3570	
بيليين	بالتبيلين	علينتيلين	ruliuli	بالتبيلين	بلينتان	بليسيلين	<u> </u>	
tgtctaaaagggcagcagtgtccatcacagggttatagaaagccacttttctcaggctgccacctgctgg 3570								
ggcggac	ccatttcaac	gtatttatgo	aaatatgtcto	cgaactaaag	tgtgtcttac	caccaaaagng	rc 3638	

Fig. 5B

10 20 30 40	·
MLRDPITITGWPPLLLLLLQLPPPPLVCGAPAGPGIGAQAS 40	·
ELWPTRLPGSASELAFHLSAFQQGFVLRLAPDASFLAPE 80	
FKIERLOGSSAAAGGEPGLRGCFFSGIVNGERESLAAMSC 120	
VACWSGSFLLAGEEFTIQPQCACDSLDQPHRLQRWGFCQR 160	
REDPGLAAAEVFPLPQGLEWEVEMGNGQQQERSINEEDRK 200	
210 220 230 240	
<u></u>	
QDKEGLLKETEDSRKVPPPFGSKTRSKRFVSEARFVETIL 240 VADASMAAFYGTDLQNHTLTVMSMAARTYKHPSTRNSVNL 280	
VVVKVLIVEKERWGPEVSDNGGLTLRNFCSWQRRFNKPSD 320	
RHPEHYDIAILFTRONFOGKGEQCDILGMADVGTICDPDK 360	
SCSVIKDEGLQAAYILAHELGHVLSMPHDDSKPCVRLFGP 400	
410 420 430 440	
MGKYHMMAPFFTHVNKFLPWSPCSAVYLITELLDDGHGDCL 440	
LDAPISVLPLPIGLECHSTLYELDQQCKQIFGPDFRHCEN 480	
TSVEDICVOLCARHRDSDEPICHTKWSSLLWADGTFCGFG 520	
HLCLDGSCVLKEDVENFKAVVDGJWGFWRFWGQCSRICGG 560	·
GIQFSNRECINEMPQNGGRFCLGERVKYQSCNIEECPFNG 600	•
610 620 630 640	
KSFREQQCEKYNAYNFFDLDGNFLQWVPKYSGVSPRDRCK 640	
LFCRARGRSEFKVFEAKVIDGTLCGPDTLSICVRGQCVKA 680	
GCDHVVNSPKKLDKOGVCGGKGTACRKISGSFTPFSYGYN 720	·
DIVTIPAGATNIDVKQRSHPGVRNDGSYLALKTANGQYLL 760]	
NGNLAISAIEQDILVKGTTLKYSGSMATLERLQSFQALPE 800	
810 820 830 840	
and the land of th	
PLIVOLLIVSGEVFPPKVRYTFFVPNLMDFSVQNSKERAT 840	
TNIIQSLPSAEWVLCIWSECPSTCRGSWQRRIVECRDPSG 880	
OASDICDEALKPEDAKECGSOECPL 905	

Fig. 6A

. 10	20	30	40		
<u> سىلىسلىسىلىس</u>	بيلينيك	بالسلب			
CGAGGGCAGAAGGCGCTI	AGCGAGCCCC	CACCGCCCCT	GGG 40		
GGCCACGAGTIAGGACCA	CCCCTTCT	GICIGAGGGG	CGC 80	·	•
TTCGTGCAGACGCTGCTC	ETGCCCAT	GCGICCATCG	CTG 120		
CCTTCTACGGGGGGGACC	TGCAGAACC	ACATCCTGAO	GTT 160		
AATGTCTGTGGCAGCCCC	EAATCTACAA	GCACCCCAGC	ATC 200		•
210	220	230	240		
سيسلسيليس	بتلتيتك	برليبيلي			
AAGAATTCCATCAACCTC	ATOGTOGTA	AAAGIGCIGA	TCG 240		
TAGAAGATGAAAAATGG	CCCCAGAGG	TGTCCGACAA	TGG 280		
GGGGCTTACACTGCGTAA	CTTCTGCAA	CTGGCAGCCG	OGT 320	·	
TTCAACCAGCCCAGCGAC	COCCACCCA	GAGCACIACG	ACA 360		
CGGCCATCCTCACCA	GACAGAACT	TCTGTGGGCA	GGA 400	•	
410	420	430	440		
<u> سىسىسىلىسى</u>	بالبنياب	بيلتستلين	سلب		
CCCCTCTCTCTCACACCCT	receile i rece	AGACATCGGG	ACC 440	•	•
ATTTGTGACCCCAACAA	VAGCTGCTCC	GTCATCCACC	ATG 480		
AGGGGCTCCAGGCGGCCC	CACACCCIGG	CCCATGAACT	AGG 520		
GCACGTCCTCAGCATGCC	CCACGACGA	CTCCAAGCCC	TGC 560		•
ACACGGCTCTTCGGGCCC	CATGGGCAAG	CACCACGIGA	TGG 600		
610	620	ഒ0	640	•	
سلسلسلسلس	سلتسلب	برليتيلي			·
CACCGCTGTTCGTCCACC	TGAACCAGA	COCTOCCCTO	GTC 640		_
CCCCTGCAGCGCCATGTT	CICAGGCIG	CCACCTGCAG	GGG 680		
TGGATCCATTTCAAGTAT	MAKATOTATITI	IGIGICICIG	AAC 720		•
TAAAGIGIGAICTTAIGC	C 739				

	10	20,	30	<u>4</u> € ·		
لحسب	uuluul	بسياست	ليستليس			
RAEGA	SEPPPPLGATS	RIKHEVSEA	RFVEILLVAD	ASMAA 40		
FYGAD	LQNHILITLMSV	AARIYKHPS:	IKNSINLMVV	KVLIV 80 .		
EDEKW	GPEVSDNGGLT	LRNFONOR	RFNQPSDRHP	EHYDT 120		
ALLT	RQNFCGQEGLC	DTLGVADIG	TICDPNKSCS	VIEDE 160		**
GLQAAI	HILAHELGHVL	SMPHDDSKP	CTRLFGPMGK	HHVMA 200		
	210	220	230	240		₹.
لسب	بالسلسب	ليتبيلين	ليتبليين	<u> </u>		
PLFVHI	NOTLEWSPCS	AMFSGCHLQ	WIHFKYLCK	CVSEL 240	•	
KCDLM	245					

Fig. 6B

Fig. 7A

10 	. 20 	30 	<u>40</u> 	50	60	70
GAAGCACCATGCAGT						
GAGCCCAGACGCCGC	GCCGCCCTG	CGCAAGGACA	GGCTGCACCC	GAGGCAAGTG	AAATTATTAG	AGACC 140
CTGAGCGAATACCAA						
ACTTCAAAAGAACGO	GACGGAGCAT	TAACICTGCC	ACTGACCCCI	GGCCTGCCTT	CCCTCCTCC	TCTTC 280
CICCICIACCICCIO	CAGGCGCAT	IACCGCCICI	CIGCCTICGG	CCAGCAGTIT	CIATTIAATC	TCACC 350
360	370	380	390	400	410	420
<u> ئىسلىسىلىسىل</u>						
GCCAATGCCGGATTT						
AGITTTATTCCGAAG						
AGCACACGGCCGTCA						
ACCAGAGCAAGAAAA						
CAACAGAGGCATTTT	MCCTTATCG	DAATAAGACG	GACAACACAA	GAGAAAAGAG	3ACCCACAGA	AGGAC 700
710	· 720	730	740	750	760	770
استاستاست	للسلسل	لتسليب	ليسلبين	ليتبلينين	لتسليب	<u> </u>
AAAACGTTTTTTTATC						
CATGGAGAAAACCTT						
GIATIGGAAATTIAA						
CATATCTTTTAATGC						
ATCCATCATGATACTO	CIGITCICIT	DAACAAGACA	GCATAICIGC	AGAGCTCACG	ACAAATGTGA	PACCT 1050
1060	1070	1080	1090	1100	1110	1120
mulmulmul	لتسليب	لتسلسب	ليستليب	لسبلسب	<u> ئىنىدلىنى</u>	<u> </u>
TAGGCCTGGCTGAAC	TGGGAACCATT	rigigatece:	IATAGAAGCT	GITCTATTAG.	IGAAGATAGI	3GATT 1120
GAGTACAGCTTTTACC	ATCGCCCATC	AGCTGGGCC	ATGIGITIAA	CATOCCICATO	SATGACAACA	ACAAA 1190
TGTAAAGAAGAAGGA	TTAAGAGTC	CCACCATGI	CATGGCTCCA	ACACTGAACT:	ICTACACCAA(CCCT 1260
GGATGTGGTCAAAGT	FIAGTCGAAA	ATATATCACIO	GAGTTTTTAG	ACACTOGTIA:	receagigi	FTGCT 1330
TAACGAACCTGAATC	ZAGACCCTAC	cilieccie	TCCAACTGCC	AGGCATCCTT.	PACAACGIGA	ATAAA 1400
1410	1420	1430	1440	1450	1460	1470
					_	
CAATGNGAATTGATT						
GCAATAACGTCAATG						
CGAGCCTGGAAACCA					-	
TCCTGGGGAAGTTGG		-				
GAGAGIGCAACACAC	CAGAACCAAA	AAATOGTGCA	AAATACTGTG	TAGGACGTAG	AATGAAATTT	AAGTC 1750

Fig. 7A (con't)

1760	, 1770	1780	1790	1800	1810	1820
ليبيلينيلينيا		لسيبليين	لسلس	لسبلسب	لسبلسب	
CTGCAACACGGAGCC	ATGTCTCAAG	CAGAAGCGAG	ACTTCCGAGA	IGAACAGIGI	SCICACITIC	ACGGG 1820
AAGCATTTTAACATC	AACGGTCTGC	TTCCCAATGI	GCGCTGGGTC	CCTAAATACA	GIGGAATTCI	CATCA 1890
AGGACCCGTGCAAGT	TGTTCTGCAG	AGTGGCAGGG	AACACAGOCT	ACTATCAGCT	TOGAGACAGA	GIGAT 1960
AGATGGAACTCCTTG	TGGCCAGGAC	ACAAATGATA	TCTGTGTCCA	GGGCCTTTGO	CGGCAAGCTC	GATGC 2030
GATCATGTTTTAAAC	TCAAAAGCCC	CGAGAGATAA	ATGCGGGGTT	TGTGGTGGCG	ATAATICITC	ATGCA 2100
2110	2120	2130	2140	2150	2160	2170
ليسلسيليس						
AAACAGTGGCAGGAA						
TACCAATATTGATGT						
AGCAGTAAAGGTGAA						
GGAATGCTGTGGTAG						
GCAAGAACTTTTGCT	TCAGGITTIG	TCGGTGGGAA	AGITGIACAA	CCCCGAIGIA	CGCTATICIT	TCAAT 2450
2460	2470	2480	2490	2500	2510	2520
ليسلسسلسم	لتشارين	ليستلينين	لتحتيليني	لتسليب	لسبلس	
ATTCCAATTGAAGAT	AAACCTCAGC	AGITTTACIG	GAACAGICAI	GGGCCATGGC	AAGCATGCAC	TAAAC 2520
CCTGCCAAGGGGAAC	GGAAACGAAA	ACTIGITIC	ACCAGGGAAT	CIGATCAGCI	TACIGITIC	GATCA 2590
AAGATGCGATCGGCT	CCCCAGCCI	GGACACATTA	CTGAACCCTG	TGGTACAGGC	TGTGACCTG	AGGIGG 2660
CATGITGCCAGCAGG	AGIGAATGIA	GIGCCCAGIG	TEECTTEEGI	TACCGCACAT	TGGACATCT	ACIGIG 2730
CCAAATATAGCAGGC	TOGATOGGA	GACTGAGAAC	GITGATCATC	GITTTTGCAG	CAGCCATCC	CAAACC 2800
2810	2820	2830	2840	2850	2860	2870
ليتبلينيلينيا						
AAGCAACCGIGAAAA						
TCAAAAAGCTGTGAC	CGTGGGACCC	CAGAGGAGAAC	GCTATTIGI	GICAATACCC	GAAATGATG	PACTOG 2940
ATGACAGCAAATGCA						
GAAATCTGGAGACTC	CTCAGAGTG	TTGGTCACCT	GIGGAAAAAGC	CCATAACCAC	CGCCAGGIC	regrer 3080
CAGTTTGGTGAAGAT	CGATTAAATC	ATAGAATGIC	FIGACCCIGAC	ACCAAGCCAA	CATCIAIGC	AGACTT 3150
3160	3170	3180	3190	3200	3210	3220
لتتبليسيانيين	ليتبليين	لستلسيا	لتسليتنا	ليسلسب	سيلس	Luul
GTCAGCAGCCGGAAT	TOTOCATOCTO	CAGGCGGG	CCCIGGGIAC	AGIGCAGIGI	CACITGIGG	ACAGGG 3220
ATACCAGCTAAGAG	CAGTGAAATG	CATCATTGGG	CTTATATGIC	'AGTGGTAGA'I	GACAATGAC	ICIAAT 3290
GCAGCAACTAGACC	ACTGATACC	CAGGACTGTG	VATTACCATCA	ATGICATCCT	CCCCAGCIG	CCCCCCGG 3360
AAACGAGGAGAAGC	ACATACAGIG	CACCAAGAACC	CACTOCCGAT	rrrecercire	GACCCCATG	CTCAGC 3430
CACTTGTGGGAAAG	FLACCCGGAT	GAGATACCIC	AGCTGCCGAG?	ATGAGAATGG	TCIGIGGCT	GACGAG 3500

Fig. 7A (con't)

3510	3520	3530	3540	3550	3560	3570
ليتبلينين	ليسلسي	uuluul	ليسلسب	لتسلبين	ليتبلينيا	
AGIGCCIGIGCIACC	CIGCCIAGAO	CAGTGGCAAA	<u> CCAACAATGT</u>	TCTGTGACAC	CCIGIGGGCA	ATGGA 3570
AGGCCTTGGACTGGA	CCTCTTCCTC	TGTGACCTGT	GGGCAAGGTA	GGGCAACCCG	GCAAGTGATG	TGTGT 3640
CAACTACAGTGACCA	CCTGATCCAT	CCCACTCACT	GTGACCAGGA	TTATATOCCA	GAAACTGACC	AGGAC 3710
TGTTCCATGTCACCA	TGCCCTCAAA	GGACCCCAGA	CAGIGGCITA	GCTCAGCACC	CCTTCCAAAA	IGAGG 3780
ACTATOGTOCCOGGA	GCGCCAGCCC	CAGCCGCACC	CATGTGCTCG	GTGGAAACCA	GIGGAGAACI	GGCCC 3850
3860	3870 -	3880	3890	3900	3910	3920
لتسليسلسي	لتسليب	لتتبليب	ليتبلينيا	لتتبيلينيا	لتستلسين	
CIGGGGAGCATGITC	CAGIACCIGI	GCTGGCGGAI	CCCAGCGGCG	TGTTGTTGLA	IGICAGGAIG	AAAAT 3920
GGATACACCGCAAAC	GACTGTGTGG	AGAGAATAAA	ACCTGATGAG	CAAAGAGCCT	GIGAATCCGG	CCCIT 3990
GTCCTCAGTGGGCTT	ATGGCAACTG	GGAGAGÌGC	ACTAAGCTGT	GTGGTGGAGG	CATAAGAACA	AGACT 4060
GGTGGTCTGTCAGCG	GTCCAACGGT	GAACGGTTTO	CAGATTTGAG	CTGTGAAATT	CTTGATAAAC	CTCCC 4130
GATCGTGAGCAGTGT	AACACACATG	CTTGTCCACA	CGACGCTGCÁ	TGCAGTACTG	GCCCTTGGAG	CTCGT 4200
4210	4220	4230	4240	4250	4260	4270
ليسلسيلسيد	لتسليب	لسبيلس	لتبتيلتين	لسلس	ليستليسا	
GITCIGICICITGIG	GTCGAGGGCA'	TAAACAACGA	AATGITTACN	GCATGGCAAA	AGATGGAAGC	CATIT 4270
AGAAAGIGATTACTG	TAAGCACCTG	GCTAAGCCAC	ATGGGCACAG	AAAGTGCCGA	CGACGAAGAT	GCCCCC 4340
AAATGGAAAGCTGGC	CCTTCCACTC	AGIGCICIGI	GICCIGIGGO	CCAGGCGIAC	AGCAGAGGCA	IGIGG 4410
GCTGTCAGATCGGAA	CACACAAAAT	AGCCAGAGAG	ACCGAGTCCA.	ACCCATACAC	CAGACCGGAG	TCGGA 4480
ATGCGAATGCCAAGG	CCCACGGIGI	CCCCTTTACA	CTTGGAGGGC	AGAGGAATGG	CAAGAATGCA	CCAAG 4550
4560	4570	4580	4590	4600	4610	4620
لسيلسلسل	لتتبيليين	لتسليب	لتبتليين	لتتتليين	ليتبليين	<u> </u>
ACCTGCGGCGAAGGC	TCCAGGIACO	GCAAGGIGGI	GIGIGIGGAT	GACAACAAAA	ACGAGGIGCA	TGGGG 4620
CACGCTGTGACGTGA	CCAAGCGGCC	GGIGGACCGI	GAAAGCIGIA	GITTGCAACC	CIGOGAGIAI	GICIG 4690
GATCACAGGAGAATG	GICAGAGIGC	TCAGTGACCT	GIGGAAAAGG	CTACAAACAA	AGGCTTGTCT	CGIGC 4760
AGCGAGATTTACACC	GGGAAAGAGA	ATTATGAATA	CAGCTACCAA	ACCACCATCA	ACTGCCCAGG	CACGC 4830
AGCCCCCCAGTGTTC	ACCCCIGITA	CCTGAGGGAG	TGCCCTGTCT	CGGCCACCIG	CAGAGITICCC	AACTG 4900
4910	4920	4930	4940	4950	4960	4970
	<u>l</u>	لتتتاييي	لببيلييي	لبيبالييي	لبيباأيين	
GGGGAGCTGCTCAGT	GICTIGIGGI	GTTGGAGTGA	TGCAGAGATC	TGTGĆAATGE	ttaaccaatg	raggac 4970
caacccagccactta						
gtgagttaccccaga						
gatgattagaggaaa						
acactggtgcatgga						

Fig. 7Å (con't)

	5260	١.	5270	5280	5290	_	300	5310	5320	
ىلىنىد	سسسب			بلينينلينيل						
GTCCCT	PODAKTA	GAGC	CCCCCC	GATGACTGCCAAT	GICGGAAC	XXATTI	ACACGG	CGCTGGGTTT	CCAG 5	320
TTTTC	GAAAATC	AGAA	TAGACC	TGACCAGCATGCA	GATAATC	ACCAC!	GACTT	ACAGTTTGCAAG	GACA 5	390
AGCGAA	AGGACATO	CCGI	CCCTTT	TGCCACAGCCGGG	CATTCCT?	ACAGO	CIGCC	AAGTGCCCACAC	EGIC 5	460
GTTTE	AGCATCAA	CTI	TATGGA	ACCGGCTTGTCTT	TAACIGA	ATCTG	CAGAI	GATATCACAAC	GGAA 5	530
TTATGO	TGICICIO	GACA	TCAAGA	AGTOGCOGGATGG	TACCCCAC	FICGIF	AGGGAA	AIGCGGIGGITA	CIGT 5	600
	5610		5620	5630	5640	_	650	5660	5670	-
				بلىسلىسل						
CCAAAA	TGCACTO	CATC	CICIGG	<u>IACTGGCCTGGAG</u>	GIGCGAGI	PTTTP:	PAGCIA	AGGIGCITIGAA	GAGG 5	670
AAGCCA	ATTATGGA.	IGGA	TGAAGG	ATAGTAATGCAAT	ACCICCAC	CTTA	ALLICC	ficcatgictat	erer 5	740
GIGIGI	GTTGIG	IGIG	ACTIGI	AIGCIIGIGIGIG	TAAATGT	TGTAC	ATATA	CATATATACA 5	804	

Fig. 7B

10 ئىيدالىيىلى	20 	30 	40 	5Ó 	60 	70 l
STADEVSWATTTITT						
FKRIRRSINSAIDPW						
FYSEEEAELKHOFYK						
TEAFSAYGNKIDVIR						
IGNLINIVIVNLIVI	HNEQDGPSIS	ENYOLLITKINE	COMOHENSEC	GIHDTAVLL	TRODICRAHD	KCDIL 350
360	370	380 .	ं १९६८	400	410	420 -
ليسلسبلسي	لتسليب	لتتبليين	لتسليب	لتستليبين	ليسلسب	
GLAELGTICDPYRSC	SISEDSGLSI	AFTIAHELGH	VFNMPHDDNN	KCKEEGVKSE	QHVMAPILNF	YINFW 420
MWSKCSRKYTTEFLD						
NVVNGVHKGCRIQHI	PWADGIECER	CKHCKXGFCV	PKEMDVPVID	GSWGSWSPFG	TCSRICGGGI	KTAIR 560
BONRPEPKNGGKYCV	GRRMKFKSON	TEPCLKQKRD	FRDEQCAHFD	GKHFNINGLL	PNVRWVPKYS	GILMK 630
DRCKLFCRVAGVIAY	YQLRDRVIDG	TPCGQDINDI	CVQGLCRQAG	CDHVLNSKAR	RDKCGVCGGD	NSSCIK 700
710	720	730	740	750	760	770
استلسلسا	لينتيلنين	ليتتأثيب				
TVAGTFNTVHYGYNT	VVRIPAGATN	IIDVROHSFSG	ETODONYLAL	SSSKGEFLLN	GNEVVIMAKR	EIRIG 770
NAVVEYSGSETAVER						
CQGERKRKLVCTRES						
KYSRLDGKTEKVDDG						
DSKCIHQEKVTIQRO						
1060	1070	1080	. 1090	1100	1110	1120
استاستاستا	ليسلسب			لىسىلىس	لىنىلىس	
QQPECASWQAGPWVQ	CSVICGOGYC	LRAVKCIIGI	YMSVVDDNDC	NAATRPIDIO	DCELPSCHPP	PAAPE 1120
TRRSTYSAPRICWRF						
ALDWSSCSVICGQGR						
YRPRSASPSRIHVLG	-					
PQWAYGNWGECTKLC			· · · · · · · · · · · · · · · · · · ·		· -	
1410	1420	1430	1440	1450	1460	1470
ليسلسيلسي	ليبيليين	لتسلسب	ليسلسن	لسياس	لستلتب	
SVSCGRGHKQRNVYC	MAKDGSHLES	DYCKHLAKPH	CHRKCROGRO	PKWKAGAWSC	CSVSCGRGVQ	ORHVG 1470
COIGTHKIARETECN						
RCDVSKRFVDRESCS						
PPSVHPCYLRECTVS						
ELPONCKEVKRLKGA						

Fig. 7B (con't)

1760 1770 1780 1790 1800 1810 1820

PYNGSRRDDCQCRKDYTAAGFSSFQKTRIDLTSMQIITTDLQFARTSEGHPVPFATAGDCYSAAKCPQGR 1820
FSINLYGTGLSLTESARWISQCNYAVSDLKKSPDGTRVVGKCGGYCGKCTPSSGTGLEVRVL.LRCFEEE 1890
AIMDG.RIVMQYLHINLGACVCVCVFVCDLYACVCKCVYTYIYT 1934

Fig. 8

HIAVISLOSOMGIFRSHDODYFIEPLOSVDEQEDEEEON 40 KPHIIYRHSTPOREPSTGKHACATSELKNSHSKDKRKIRM 80 PKRRKRNSLADDVALLKSGLATKVLSGYSNOINNIRDRWN 120 HERTKRELSYPREVEVMVVADHRMVLYHCANLOHYTLTLM 160 SIVASIYKOSSIGNLINIVIVNLVVIHNEQEGPYINFNAQ 200 TTLKNFCQWQHSKNYLGGIQHDTAVLVTREDICRAQDKCD 240 TLGLAELGTICDPYRSCSISEDSGLSTAFTIAHELGHVFN 280 MPHDDSNKCKEEGVKSPOHVMAPTLNFYINPWMWSKCSRK 320 YTTEFLDTGYGECLLNEPASRTYPLPSQLPGLLYNVNKQC 360 ELIFGPGSQVCPYMMQCRRLWCNNVDGAHKGCRTQHTPWA 400 DGTECEPGKHCKFGFCVPKEMEGPAIDGSWGGWSHFGTCS 440 RICGGGIKTAIREONRPEPKNGGKYCVGRRMKFKSCNTEP 480 CMKQKRDFREEQCAHFDGKHFNINGLLPSVRWFPKYSGIL 520 MKDRCKLFCRVAGNIAYYQLRDRVIDGIPCGQDINDICVQ 560 GLCRQAGCDHILNSKVRKDKCGICGCENSSCKIVAGIFNI 600 VHYGYNIVVRIPACATSIDVRQHSFSGKSEDDNYLALSNS 640 KGEFLLNGDFVVSMSKREVRVGSAVIEYSGSINVVERLNC 680 TDRIEEELLLQVLSVGKLYNPDVRYSFNIPIEDKPQOFYW 720 NSHGPWQACSKPCQGERRRKLVCTRESDQLTVSDQRCDRL 760 PQPGPVTEACGTDCDLRWHVASKSECSAQCGLGYRTLDIH 800 CAKYSRMDGKTEKVDDSFCSSQPRPSNQEKCSGECSTGGW 840 RYSAWTECSRSCDGGTQRRRAICVNTRNDVLDDS 874

Fig. 8 (con't)

360	370 ·		390	400	410	<u>4</u> 20
ليستلسيلسيا	بليسيلين	للتسليين	لبيبليب	لسسلسب	uuluul	
ACAGATOGAACCACA	AAAGAACCAA!	CCCTTCIC	ICCIACCCAC	CCTTICUAGA	SCICAICCIC	GTGGC 420
TGACCACAGGATGGT	TTATACCACC	GAGCAAACC	ITCAACATTA	TATCTTAACC	MAATGICCA	TIGIA 490
GCTTCTATCTATAAA	GACTCAAGEA	TTTAAAEDTT	TTATAATTAA	GITATIGIGA	ACTIAGITGI	GATTC 560
ATAATGAACAGGAAG	GACCITACATA	AATTTCAAT	GCCCAGACAA	CATTAAAGAA	TTTTTGCCAG	TGGCA 630
GCACTCAAAGAACTA	CTTGGGTGGG/	ATTCAGCACG	ACACAGCCGI	TCIGGICACA	AGGGAAGATA	ICIGC 700
710	720	730	740	750	760	770
لىسلىسلىس	لسبلس	لسبلين	لبسلسب	لسيلس	لبينليبيا	
AGAGCTCAGGACAAA	TGTGACACCT	PAGGICTICC	IGAACIGGGA	ACCATITGCG	ACCCCTACCG	AAGCT 770
GTTCCATTAGTGAAG	ACAGTGGGCT	GACACAGCT	TICACAATAC	CTCACGAGCT	GGCCATGIG	TTTAA 840
TATCCCTCACGATGA	CAGCAATAAA.	ICCAAAGAAG	AAGGAGITAA	CACTCCCCAG	CAIGICAIGG	CACCA 910
ACACIGAACTICIAC	ACCAACCCCI	CATGIGGIC	aaagigcagi	CGGAAATACA'	ICACIGAGI'I	CCTAG 980
ACACTGGGTACGGAG	AGTGCTTGCT	GAATGAACCT	GCATCCAGGA	CCIAICCITI	GCCTTCCCAA	CIGC 1050
1060	1070	1080	1090	1100	1110	1120
<u></u>	لتستلين	لتستليب	ليتتليين	لسيلس	لبيبليين	
CCCCTTCTCTACAA	CCTCAATAAA	CAATGTGAAC	TGATTTTTGG	GCCAGGCICI	CAAGIGIGCC	CCTAT 1120
ATGATGCAGTGCAGA	COGCTCTOGT	CAATAATGT	GGATGGAGC?	CACAAAGGCT	GCAGGACTCA	GCACA 1190
CCCCTCGGCAGATC	GAACCGAGIG	TGAGCCTGGA	AAGCACIGC	AGTTTCGATT	TIGIGITCCC	AAAGA 1260
AATGGAGGGCCTGC	'AATTGATGGA'	TCCTGGGGAG	CITCGACCC	ACTITICGGACC	IGCICAAGAA	CGIGI 1130
GCAGGAGGCATCAAA	ACAGOCATCA	GAGAGIGCAA	CAGACCAGAC	OLAAAAAOOC	GIGGGAAGI	ACIGIG 1400
1410	1420	1430	1440	1450	1460	1470
ليسلسلسل	لبسابين	لسسلس	سساست	لسلسل	····	
TAGGAAGGAGAATG	AGTTCAAATC	CIGCAACACC	GAGCCCIGC	ATGAAGCAGAA	GCGAGACTI	CCACA 1470
GGAGCAGTGTGCTC	CTTTGATGGC	AAACACTICA	ACATCAATC	FICIGCIGCC	AGCGLACGC	IGGITT 1540
CCTAAGTACAGCGG	ATTITGATGA	AGGACCGGTC	CAAGITGIT	TICCAGAGIC	CAGGAAACAC	CAGCCT 1610
ACTACCACCTCCGAC	ACACAGTGAT	TGACGGAACC	CCTIGICGC	CAGGACACAA	IGACAICIG.	IGICCA 1680
AGGCCTTTGCCGGC/	AGCTGGATGI	GATCATATTI	TAAACTCAA	AGGICCGGAAA	GATAAAIGI	333A11 1/50
1760	1770	1780	2.50	1800	1810	1820
	لتسلسنا	لتستليب	سنسلسب	Luuluu	<u> </u>	1020
TGIGGIGGAGATAA	TTCTTCATGC?	AAACAGIGG	CAGGAACATT	TAACACIGIC	ATTAIGGIT	ACAATA 1820
بلبية لا تحجيب المناسبين	ATTENDED TO THE	TACCAGCAT	IGACGIGCGI	CAGCACAGCI'	ICICAGGGAA	GICIGA 1650
CONTRACT ACTIVITY	بكلامينينكونا	AAACTEDADAA	GTGAATTCC	ICCTAAATG	ACACTITOTI	GICICC 1300
מבבבטע ע ע פירוניגענע	كالكاكاكالاللاك	TGCAGCGCCG	ICATIGACIA	CAGCGGAILCG	EACAATG166	AIGGAMM SOOO!
GACTGAACTGTACG	GACCGIATCG	AGGAAGAACT	ICICCTICAG	GIGITGICCG	I JEJAAASEE I	GIMIMM ZIUU

Fig. 8 (con't)

	2110	2120	2130	2140	2150	2160	2170
لسب		ببلينيلين	ببليستليب	بيلينينلين	سلسسلت	بالتسليب	<u>l.</u>
CCCAG	ATGTGCGGTAC	CATTCAATAT	TCCCATTGAG	GACAAACCTC	'AGCAATTITA	CTGGAACAGT	CAC 2170
cccccc	TIGGCAAGCAT	CAGCAAGCCC	TGCCAAGGG	AGCGGAGACG	AAAACTTGTT	TGCACCAGG	AGT 2240
CTGATO	CAGCTAACCGT	TCTGATCAAA	GATGTGACCC	GCTGCCCCAG	CCAGGACCIG	TCACTGAAGC	GTG 2310 ·
CCCCAC	CAGACTGTGACT	TGAGGIGGCA	LCGTTGCCAGC	'AAGAGCGAAT	GCAGTGCCCA	GIGIGGITIG	GGC 2380
TACCG	PACTITAGACA1	CCACTGTGCC	'AAATACAGCA	GGATGGACGG	GAAGACGGAG	AAGGIGGATG	ACA 2450
	2460	2470	2480	2490	2500	2510	2520
للتبيد	سلسسلس	ببلينيلين	بيلتسلين	بيلينينلين	بيليينيلين	بالبياب	<u></u>
GITTCI	IGTAGCAGTCA	LCCCAGACCGA	GTAACCAGGA	GAAATGCTCA	GGAGAGTGCA	GCACAGGTGG	ATG 2520
GCGCIZ	ATTCAGCCTGG#	CCGAATGTTC	TAGAAGCIGI	CATGGTGGTA	CCCAGAGAAG	AAGAGCAATT	TGT 2590
GTCAAC	CACCCGCAATGA	TETTETTET	GACAGCAA 2	625			

Fig. 9A

10	. 20	30	40	50	60	70 ·	
سيبلسيلسب	ليبيليينا	سيبليب	لتبتليينا	لتتبليينا	لتتبليين		_
TCACGCACGCCTTC	CGICICAAGAI	GAGTTCCT	FICCAGICIG	AGACCTATGA	GATCGCCTTC	CCCAC 70	
CCGCGTGGACCACA							
GGGCCACAGCCGAG:	recesserrerre	TACAAACT	GCCTCGCCAC	CACCCACTIC	CTGCTGAACC	TGACC 210	,
CCCVCCICCCCCICIA	ACTEGCAGEGG	CGTCTCCG	IGGAGI'ACIG	ACACGGGAGG	GCCIGGCCIG	CCAGA 280	
ecccccccccccc	CACIGCCICTÁC	GCTGGTCA(CTGCAGGGCC	'AGGCCAGCAG	CICCCAIGIC	GCCAT 350	
360	370	380	390	400	41 0 .	420	
المسلمسليسين	بلتتتيليتينا	لتستليب	لتسليسا	لتسليب	لتتتبليين		_
CAGCACCTGTGGAG	CCTGCACGGCC	TGATCGIC	CAGACGAGGA	AGAGTACCTG	ATTGAGCCCC	TGCAC 420	
GGIGGGCCCAAGGG	TTCTCGGAGCCC	GGAGGAAAC	TOGACCACAT	GIGGIGIACA	AGCGITCCIC	TCTGC 490	
GICACCCCCACCIG	EACACAGCCIGI	GCAGIGAG	AGATGAGAAAC	CGTGGAAAGG	CCCCCATGC	TGGCT 560	
GCGGACCTTGAAGCC							
CGATCGGTCAGCCG	AGAGCGCTIACGT	GGAGACCCI	GGIGGIGGCI	GACAAGATGA'	ICCICCCIA	ICACG 700	
710	720	730	740	750	760	770	
ليتتلينينا	ىلىسىلىسىا	لتسليب	ليتبليننا	لتتنابينا	لستلسب		- .
GGCGCCGGGATGTGC	AGCAGIAIGIC	CIGGCCAIC	ATGAACATIC	TTGCCAAACT	TTTCCAGGAC	TCGAG 770	
TCTGGGAAGCACCG	TAACATCCTCC	TAACTCGCC	CICATCCIGCI	CACGGAGGAO	CAGCCCACTC	TGGAG 840	
ATCACCCACCATGC	COGGAAGICCCI	'AGACAGCT'	CTGLAAGIGG	CAGAAATCCA	TCGTGAACCA	CAGCG 910	
GCCATGGCAATGCC	ATTCCAGAGAAC	GGTGTGGCT	TAACCATGACA	CAGCAGIGCI	CATCACACGC	TATGA 980	
CATCTGCATCTACA	AGAACAAACCCT	GCGGCACAC	TAGGCCTGGC	:CCGGIGGGCG	GAATGIGIGA	.cccc 1050	
1060	1070	1080	1090	1100	1110	1120	
ليسلسلسل	باستبلتست	لتنتليين	ليستلسنا	لبسيلست	لتستليبنا		-
AGAGAAGCTGCAGCC	FICAATGAGGAC	ATTOGCTCC	CACAAGCGII	CACCATTGCC	ACGAGATCGC	GCACA 1120	
CATTCGGCATGAACC	CATGACGGCGTG	CGAAACACC	TGTGGGGCCC	GIGGICAGGA	CCCAGCCAAG	CTCAT 1190	
GGCTGCCCACATTAC	CATGAAGACCA	ACCCATTCC	TGTGGTCATC	CIGCAACCGI	GACTACATCA	CCACC 1260	
TITCTAGACTCGGGC	cieeecicie	CCTGAACAA	rccaecacicac	'AGACAGGACT	TTGTGTACCC	GACAG 1330	
TGGCACCGGGCCAAC	OCTACGATGCA	GATGAGCA	AIGCCGCÌTIC	'AGCATGGAGT	CAAAICGCGI	CAGIG 1400	
1410	1420	1430	1440	1450	1460	1470	
ليسلسيلسا	بسيبينين	لتتتبليين	لتسلسنا	لسطست	لتستليب	ــــــــــــــــــــــــــــــــــــــ	-
TAAATACGGGGAGG	CTGCAGCGAGC	TCTCCTCT	TGAGCAAGAC	CAACCGGIGC	ATCACCAACA	GCATC 1470	
CCCGCCCGCCCACGGC	CACGCTGTGCCA	GACGCACAC	CATCGACAAC	CCCTCCTCCT	ACAAACGGGI	CIGIG 1540	
TCCCCTTTGGGTCGC	CCCCAGAGGGI	GIGGACGC	ACCCIGGGGGC	CGTGGACTCC	ATGGGGCGAC	TGCAG 1610	
CCCCACCTGTGGCGC							
AAGTACTGTCTGGG	TGAGAGAAGGCC	CCACCGCTC	CTGCAACACC	CATCACIGIC	CCCCIGGCIC	CCAGG 1750	

Fig. 9A (con't):

1760 1770	1780	1790	1800	1810	1820
ACTICAGAGAGTGCAGTGTTCT					
GTACCGGGGGGGGGGGGGGGAAGG					
ACCCCCACCCTCTTCCACCC					
GCAAGCACGTGGGCTGCGACCGA					
TGACGGCAGTGCCTGCGAGACCA					
. 2110 2120	2130	2140	2150	2160	2170
GTCGTCTGGATTCCCAAAGGCTC	•				•
CCCTGAAGGGAGACCAGGAGTCC					· -
TCTAGCTGGGACCACCTTTCAAC					
ATTAATGCATCTCTCATCGTCAT	GCTGCTGGCCCGC	ACCGAGCTG		CCTACCCCTT	
CCCCCATCGCCCGTGACTCGCTG	CCCCCCTACTCCT	GGCACTATG	CCCCTCGAC	CAAGIGCICG	GCCCA 2450
2460 2470	2480	2490	2500	2510	2520
بينا بينيا بينيا بينيانين	بليستلينين	لتسلبين	لنسلبب	<u></u>	
GIGIGCAGGCGGTAGCCAGGTGC	ACCCCCTCCACTC	CCGCAACCA	CTGGACAGC	TCCGCGGTCG	CCCCC 2520 ·
CACTACTGCAGTGCCCACAGCAA	GCTGCCCAAAAGG	CAGCGCGCC.	TGCAACACGC	AGCCTTGCCC	TCCAG 2590
ACTOGGTTGTAGGGAACTGGTCG	CTCTGCAGCCGCA	GCTGCGATG	CAGGCGTGCC	CAGTOGCTOG	GICGI 2660
GTGCCAGCGCCGCGTCTCTGCCG	CGGAGGAGAAGGC	CCTGGACGAC	CAGCGCATGC	.CCGCAGCCGC	GCCCA 2730
CCTGTACTGGAGGCCTGCCACGG	CCCCACTTGCCCT	CCGGAGIGG	CAACCCICC	ACIGGICIGA	GIGIA 2800
2810 2820	· 2830	2840	2850	2860	2870
<u>سيابي بالسيابيي</u>	بليستليسي	ليسابين	لتستليب	لتسلسيا	ــــــــــــــــــــــــــــــــــــــ
CCCCAAGCTGTGGGCCTGGTCTC	CGCCACCGAGTGC	FICCITIGIA	AGAGTGCAG	ATCAACGATCI	ACTCT 2870
GCCCCTGGGCACTGCCTTCCTG	CAGCCAAGCCACC	ATCIACIAT	CCATCIAAC	TTGCGCCGCT	GCCCT 2940
CCTGCCCGCTGGGTGACCAGTGA	GIGGGGIGAGIGI	TCCACACAG	IGTGGCCTCC	3GCCAGCAGCA	GCCCA 3010
CAGTGCGCTGCACCAGCCACACC	GGCCAGCCATCIC	CAGAGICCA	CIGAAGCCII	TGCGGCCATCC	ACCAT 3080
GCAGCAGTGTGAGGCCAAGTGTG	ACAGIGIGGIGCC	GCCIGGAGA:	TGGCCCAGA2	AGAATGCAAGG	ATGIG 3150
3160 3170	3180	3190	3200	3210	3220
سلسيباسياسيلس	<u>ىلىنىلىنىك</u>	ليبيلين	لتسليب	لينتطينينا	
AACAAGGIGGCTTACIGCCCCCI	GGIGCICAAATTI	CAGTICIGE	AGCCGAGCCT	L'ACTICCGCCA	GATGT 3220
GCTGCAAAACCTGCCAAGGCCGC	tagggtacctgga	accaacctg	gagcacaggo	tgaggcaggg	gacat 3290
cccactggagagggcatgaggga	aag gggg gcttga	attgaaggg	tgagatgcag	gttgaaagtta	itttat 3360
tgggtaaccctacagggctcctg	ractaaggggtgga	agaagagctg	gctacccagg	ggaccctctgc	tgtat 3430
cttgcccagttgatagtgaagag	ragaggactccttg	gttgcacaca	tatttaagto	cctagcacco	ctccc 3500

Fig. 9A (con't)

3510	352	20 3530	3540	3550	3560	3570	
بليتيلينين	لتستليب	سلسسلس	سلسسلب	سلسسلت	ببليسلين		
accetttgato	gaatatgt	actgtgaagagt	gggggtgggg	aggggtgtgc	tggtgccctgc	cccctgc 35	570"
actgttctatc	ctacactc	tgagctgggggg	atttatatct	gctatg ggg g	gagtaggcttg	rataccac 36	540
ctccctgtagc	ctcccca	gactgacgaagg	ggaagatcca	cccaaccto	tgccctgcctg	rccccagg 37	710
ggggagttcaa	atccaggo	cgttccccatca	itggtgctaca	agecetgeee	tggggcccaca	cacteet 37	780
caccaagaagc	ttacatta	aaaaagttgtgt	tatcctacaa	aaaaaaaaaa	aaactcgaggg	ggggccc 38	350
3860	387	0 3880	3890	3900	3910	3920	2
<u> باينيىلىيىلى</u>	لتستليب	بلينيلين	<u> بىلىرىلىر</u>	<u>بىلنىيىلى.</u>	بتبليبيلين	<u>ılıııl</u>	
ggtacccaatte	ococtata	otaaatnoootn	tta 3885		•	•	٠.

Fig. 9B

10	20 30	<u>4</u> 0 .		
- -	Linding L			
SRIPSGLKMSSCPVWRAM				
CAAPRHOCHSRVPPLLQS	GLASTHFLLNLTRSSRLI	ACRV 80		
SVEYWIREGLAWQRAARP	HCLYAGHLQGQASSSHVA	ISTC 120		
GGLHGLIVADEEEYLIEP	LHGGPKGSRSPEESGPHV	VYKR 160		
SSLRHPHLDTACGVRDEK	PWKGRPWWLRTLKPPPAR	PLON 200		
	220 230	240		,
andred parker.	donatura la reco	التا	-	·
ETERCOPCLKREVSRERY	ÆTLVVADKYMVAYHGRR	DVEQ 240	·	
YVLAIMNIVAKLFQDSSLO	SIVNILVIRLILLTEDO	PILE 280		
ITHHAGKSLDSFCKWQKS				
VLITRYDICIYKNKPCGT				•
AATSVHHCHEIGHTFGMV	-IDGVGNSCGARGQDPAKI	MAAH 400		
	120 430	440		
بيبليبيليين	_, _,			
ITMKINPFVWSSCNRDYIT				
YPTVAPGQAYDADEQCRFQ				
KSNRCITNSIPAAEGTLO			•	
EGVDGAWGFWIFWEDCSRI			•	
KYCLGERRRHRSCNIDDCI			•	
•	520 630	640		
mulmulmal, , , , , , , , , , , , , , , , , , , 				•
KFYKWKTYRGGGVKACSLI	SLAEGFNFYTERAAAVVI	CTP 640		
CRPDIVDICVSGECKHVGC				
ACETIEGVFSPASPGAGYE				
SHLALKGDQESLLLEGLPG				•
QVQSLEALGPINASLIVM				•
	820 830	840	•	
سيلسلسلس				
LPPYSWHYAPWIKCSAQCA				
HYCSAHSKLPKRORACVTE				
VRSRSVVCQRRVSAAFEKA				
CPPEWATLDWSECTPSCGE				
HCLPAAKPPSIMRCNLRRC				

Fig. 9B (con't)

	1010	1020	1030	1040			
	استاستاست	ببيليين	ليبيلينيا	Luul	 ·	 	_
•	QQRIVRCTSHTGQPS	RECTEAL RP	SIMQQCEAKCI	SVVPP 1040			
	GDGPEECKDVNKVAY	CPLVLKFQF	CSRAYFROMCC	KTCQG 1080	•	•	
	R 1081						

Fig. 10A

	10	20	30	40				
	3000000							
	AGCAGCAGCTGTGG							
	ACGGIGGACATTIG							
	GCTGTGACAGGGTC				•			2
	ATOCCGIGIGIGIG		•					
	ATTGAAGGTGTCTT	TAGCCCAGCT	MIGCCAGGAA	CIGGGT 200				·
	210	220	230	240				
						·		
	ATGAGGACGTCGTC					٠.		
	TTTCATCCAAGATC				•			
	CTAAAGGGGGACCA						-	
	CTCCCAA				•			
	CACATTTCATCTAC	GGCAGGGGCCC	3GACCAGGCA	CAGAGC 400				•
	410	420	430	44 0				
	سيلسيلسب	لتتتبليتيط	بتبيليتيا	ـــــلىنىك				
	CTGGAAGCCCTGGG	ACCCATTAATC	CATCICICA	TCATCA 440				
	TGGTGCTGGCCCAG	GCAGAGTTGCC	TIGOTOTOCA	CTACCG 480				•
•	CTTCAATGCACCCA	TTGCCCGGGAI	IGCACIGCCI	CCCTAC 520			-	
	TCCTGGCACTATGO	CCCCIGGACCA	AATGCTCAG	CCCAGT 560				
	GTGCAGGCGGCAGC	CAGGTCCAAGT	PAGTGGAGTG	CCGAAA 600				
	610	620	ഒ0	640				.,
		ليسلسين	سيلسب	ــــــا			<u>.</u>	
	TCAGCTGGACAGCT	CAGCAGTGGCC	CCACACTAC	TGTAGT 640				•
	GGCCACAGTAAATT							
	CAGAACCATGTCCA	CCAGATIGGGI	TGTAGGAAA	CIGGIC 720				
	ACGCTGCAGCCGTA						•	
	TCAGIGGIGIGCCA							
	810	820	830	840				
	·	1						
	AAGCCITAGACGAC	AGTGCCTGTCC	CACAGCCACG	CCCACC 840				
	TGTGCTGGAGGCCT	GCCAAGGCCC	AIGIGCCCT	CCTGAG 880				
	TGGGCAACCCTCGA	CIGGICIGAGI	IGIACCCCAA	ectigig 920			•	•
	GCCIGGICICCGC	CACCGACTOGI	CCTTTGTAA	CACTOC 960				•
	AGATCAACGATCIA	cicicoccci	reegcacieo	CTTCCT 1000)			

Fig. 10A (con't)

1010 1020 1030 1040	
GCAGCCAAGCCACCATCTACTATGCGATGIAACTTGCGCC 1040 GCTGCCCTCCTGCCCGCTGGGTGACCAGTGAGTGGGTGA 1080	
GIGITCCACACAGIGIGOCCICOGCCAGCAGCAGCACCACA 1120 GIGCGCIGCACCACCACACCACCACCATCICGAGAGI 1160 GCACIGAAGCCITGCGCCATCCACCATGCAGCAGIGIGA 1200	
1210 1220 1230 1240	
GCCCAAGTGTGACAGTGTGCCGCCTGGAGATGGCCCA 1240 GAAGAATGCAAGGTGTGAACAAGGTGGCTTACTGCCCCC 1280 TGGTGCTCAAATTTCAGTTCTGTAGCCGAGCCTACTTCCG 1320	
CCAGATGICCIGCAAAACCTGCCAAGGCCGCTAGGTTACC 1360 TGCAACCAACCTGGAGCACAGGCTGAGGCAGGGGACATCC 1400	·
1410 1420 1430 1440	
CACTOGAGAGGGCATGAGGCGAAAGGGGGGCTTGAATTGAA	
TGAAGAGAGACTTCTTGGTGNACACATTTTTAAGTCC 1600 1610 1620 1630 1640	:
TTAGACCCTTCCACCNTTGATCGGATATGTCTGGGAAGAG 1640 GN 1642	

Fig. 10B

	10	20	30	40
للتبيد	ليستليب	<u>سياست</u>	ليبيابينا	لبييا
AAAVVI	CTPCRPDIV	DICVSGECK	NGCDRVLGST	ILREDK 40
CRVCCC	EDGSACETIE	GVFSPALPG	GYEDVWIPK	CSVHI 80
FIQDLA	ULSLSHLALK	GEOGESLLLEC	LPGTPQPXRL	PLXGT 120
			IMVLAQAELE	
			QCAGGSQVQV	
	210	220	230	240
بليبيد	<u> </u>	ليستلبب	<u></u>	
QLDSSA	.VAPHYCSGH	SKLPKRQRAC	NTEPCPPDW	VONWS 240
			EKALDDSACP	
			CGPGLRHRVV	
			RRCPPARWT	
			ECTEALRPST	
	410	420	430	440
ىلىب	لسبلسا	ليبيليب		ــــــــــــــــــــــــــــــــــــــ
AKCDSV	VPPGDGPEE	KDVNKVAYC	PLVLKFQFCS	RAYFR 440
	COGR 450	•		

Fig. 11A

Ligated 459225+482392 with Sac I(168)&Eco RI(or Not I) Cloning site:5';Eco RI 3';Not I Vector; PT7T3 pac.

You can put this construct to pcDNA3.1(+) for transfection 5'-UTR is 50bp &3'-UTR is 175bp

210-215; in 482392 it's TCCTAC(SY).

		•	•	3		
10	20	30	40	•		•
ا بىنىلىنىد	uuluu	liiiliii				
gaatteggeaegagg	cagtgtccg	attctgattc	cggcaa 40		•	
ggatccaagcATGGA	ATGCTGCCG	TOGGGCAACT	cciocc 80 .			•
				•		
GGACCGCACgctCCG	AGGAGGACC	GGGACGGCCI	ATGGGA 160			
210	220	230	240			
		1,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	لىنىل	· · · · · · · · · · · · · · · · · · ·		
GCTGCGGCCGCCAAC	TCTCTCAGC	CCCTCCCTGA	GCAGCA 240			•
				•	Ÿ	•
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		•				•
610				·		· .
						
ACTIVITATOTOGAA TGAAAACAGTOTOA						
	gaatteggeaegagg ggatecaageATGA ACACTGCTGCTCTTT GGACCGCACGetCGG TGCCTGGGGCCCCATG 210 LILLLILLL GGTGGGGCCGCCAAC AGACCTGTGAAGGAA TAATGTGGACTGCCC CAGCAATGCTCAGCT AGTTTTATGAATGGC GTTGTTGAACTAAC GTTGTTGAACTAGCA GTTGTTGAACTAGCA GCTATACAGAATCTT CCAAATTGTTGGCTC AAGGAAGATAACTGT CCGCAGCTGGTCC CGCAACCAAATCGGAAC GCGAACTAGACATATT ACTTATATCTGGAA	gaatteggeacgaggeagtgteeg ggateeaageATGAATGCTGCGG ACACTGCTCCTTTCTGGCTTTC GGACCGCACGCCCACGAGGAGCAC TGCCTGGGGCCCATGCAGTGAATG 210 220	gaattcggcacgaggcagtgtccgattctgattc ggatccaagcaTcGAATCTGCGGTCGGCAACT ACACTGCTCGTTTTCTGGCTTTCCTGCTCGGCACC GGACCGCACGCCCAGGAGGAGGACGCCCCTGAGGCCCCATGCAGTGAATGCTCACGCACC 210 220 230 GGTGGGGCCGCCAACTCTCTGAGGCGCTGCCTGA ACACTGTGAAGCAACTCTCTGAGGCGCTGCCTGA ACACTGTGAAGCAACAACTCTCTGAGGCGTGCATTTC CAGCAATGCTCAGCTCA	gaatteggeacgaggeagtgteegattetgatteeggeaa 40 ggatecaageATGAATGCTGCGTGGGCAACTCCTGC 80 ACACTGCTCCTCTTTCTGGCTTTCCTGCTCCTGAGTTCCA 120 GGACCGCACGECCGAGGAGGACGCCCTATGGGA 160 TGCCTGGGGCCCATGCAGTGAATGCTCACGCACCTGCGGG 200 210 220 230 240 GGTGGGGCCCGCAACTCTCTGAGGCGCTGCCTGAGCAGCA 240 AGACCTGTGAAGCAACAACATCACGAGACAACATGCAG 280 TAATGTGGACTGCCCACCAGGAAGCAGGTCATTTCCCAGCT 320 CAGCAATGCTCACCTCATAATGATGTCAAGCACCATGCCC 360 AGTTTTATGAATGCCTTCCTGTGTCTAATGACCCTGACAA 400 410 420 430 440 CCCATGTTCACTCAAGTCCCAAGCCAAAGCAACACCTG 440 GTTGTTGAACTACCACCTAAAGTCTTAGATGGTCACGCTT 480 GCTATACAGAATCTTTGGATATGTGCATCAGTGGTTTATG 520 CCAAATTGTTGGCTGCGATCACCAGCTGGAAGCACCGTC 560 AAGGAAGATAACTGTGGGGTCTGCAACGCAAACCACGTC 560 CCAAATTGTTGCCTGCGATCACCAGCTGGGAAGCACCGTC 560 CCCAACTAACTGTGGGGTCTGCAACGGAGATGGTCCA 600 610 620 630 640 CCTGCCGGCTGGTCCGAGGGCAGTATAAATCCCAGCTCTC 640 CCCCAACCAAATCGGAGGAGCAACAACCTAT 680 GCAAGTAGACATATTCGCATTGTGTTTAAAAGGTCCTGATC 720 ACTTATATCTGGAAACCAAAACCCTCCAGGGGACTAAAGG	gaatteggeacgaggeagtgteegattetgatteeggeaa 40 ggatecaageATGCAATGCTGCGTCGGGGAACTCCTGGC 80 ACACTGCTCCTTTTCTGGCTTTCCTGCTCCTGAGTTCCA 120 GGACCGCACGECCCAGGAGGACGCCCCCAGGCCCTATGGCA 160 TGCCTGGGGCCCATGCAGTGAATGCTCACGCACCTGCGGG 200 210 220 230 240 CTICCGGCCCCCAACTCTCTCAGGCCCTCCCTGAGCAGCA 240 ACACCTGTGAAGCAACAACTCTCTCAGGCCCTCCCAGCAGCAC ACACCTGTGAAGCAACAAATATCCGATACAGAACATCCAG 280 TAATGTGGACTGCCCACCAGAAGCAGGTGATTTCCCAGCT 320 ACGTTTATCAATGCCTTCCTGTGTCTAATGACCCTGACAA 400 410 420 430 440 CCCATGTTCACTCAAGTGCCAAGCCAAAGCAACACCCTG 440 GTTGTTGAACTACGCCCTCAAGGTCTTACATGGTACGCGTT 480 GCTATACAGAATCTTTGGATTATGTGCATCAGTGGTTTTATG 520 CCAAATTGTTGCTGCGATCACAGCTGCAACCACCGTC 560 AAGGAAGATAACTGTGGGGTCTGCAACGCAACCACCGTC 560 CCAAATTGTTGCCTGCGACGCACCCAACCAACCAACCACCGTC 560 CCCAACTAACTGTGGGGTCTGCAACGCAACCACCTTCC 640 CCCCCCCCCCCTGTGCCAGCGCCAAGTTCCCAGCTCTCTC 640 CCCCCCCCCCCTGTGCCAGCGCCAATGCTTCCAATCCCTCTCT 680 CCCCCAACTAATTCGCCTTGTGTTTTAAAACGTCCTGATC CCCCAACTAATTCGCCTTGTGTTTTAAAACGTCCTGATC CCCCAACTAATTCGCCTTGTGTTTTAAAACGTCCTGATC CCCAACTAAATCGGTTGATACTGTGGTTTCCAACTCCTATC CCCAACTAAATCGGTTCAACCCTTGTGTTTAAAACGTCCTGATC CCCAACCAAATCGGTTCATCACCTTGTGTTTAAAACGTCCTGATC CCCAACCAAATCGGTTCAAACCCTTCCAGGGGACTTAAAGG CCCAACCAAATCGGTTCAAACCCTTCTCAACGGACCTTCAACGG CCCAACTAAATCGGATCATTACTGTGGTTTCCAACTCCTGATC ACTTTATATCTGGAAACCAAAACCCTTCCAGGGGACTTAAAGG CCAACTAAATCGGATCATTATCGCCTTTTTAAAAACGTCCTGATC ACTTTATATCTGGAAACCAAAACCCTTCCAGGGGACTTAAAGG ACTTTATATCTGGAAACCAAAACCCTTCCAGGGGACTTAAAGG ACTTTATATCTGGAAAACCAAAACCCTTCCAGGGGACTTAAAGG ACTTTATATCTGGAAACCAAAACCCTTCCAGGGGACTTAAAGG ACTTTATATCTGGAAAACCAAAACCCTTCCAGGGGACTTAAAGG ACTTTATATCTGGAAAACCAAAACCCTTCCAGGGGACTTAAAGG ACTTTATATCTGGAAAACCAAAACCCTTCCAGGGGACTTAAAGG ACTTTATATCTGGAAAACCAAAAACCCTTCCAGGGGACTTAAAGG ACTTATATCTGGAAAACCAAAACCATCCCTCCAGGGGACTTAAAGG ACTTATATCTGGAAAACCAAAACCCTTCCAGGGGACTTAAAGG ACTTATATCTGGAAAACCAAAACCCTTCCAGGGGACTTAAAGG ACTTATATCTGGAAAACCAAAACCATCCCCCCAGGGCACTTAAAGGGTCTGATCAACACAACCATTATTCGCCTTTTAAAACCTTCCAGGGACCTTCAACGGACCTTCAACGGACCTTCAACGGACCTTCAACGGACCTTCAACACTTCAACACTTCCAGCTTCAACACTTCCAGCTTCAACACTTCCA	gaatteggeacgaggeagtgteegattetgatteeggeaa 40 ggateeaageArtgAArtocteectgTcGGCAACTCCTGC 80 ACACTGCTCCTTTTCTGGCTTTCCTGCTCTGAGTTCCA 120 GGACCGCACGGCACGACAGGACGGCACGGCCTATGGGA 160 TGCCTGGGGCCCATGCAGTGAATGCTCACGCACCTGCGGG 200 210 220 230 240 210 220 230 240 GGTGGGGCCCCAACTCTCTGAGGCGCTGCCTGAGCAGCA 240 AGACCTGTGAACGAACAACTCCAGC 280 AGACCTGTGAACGAACAACAACAACAACACACCAC 280 TAATGTGGACTCCCACCAGAACCAGGTCATTTCCCAGCT 320 CACCAATGCTCACCTCATAATGATGCAACACCACCACAA 400 410 420 430 440 410 420 430 440 CCCATGTTCACTCAAGTCCCAACCAAAGCAACACCCTG 440 GTTGTTGAACTACACACCAAAGCAAACAACCCTG 440 GTTGTTGAACTACACACCAAAGCAACACCACTG 480 GCTATACAGAATCTTTGCATATGTCCAACGTCTTAGTTTTATG 520 CCAAATTGTTCCTGCAACGCAAAGCAACACCCTG 560 AAGGAACATACTTTGCATCACTGCGAACCACAGCTCTC 640 CCCAACCAAATCGTGCGACCAACGCAACGACACCTCTC 640 CCCCAACCAAATCGTCCAACGCAACGAACAATCCCTCTC 640 CCCCAACCAAATCGTCCAACGCAACGAACAATCCCTCTC 640 CCCCAACCAAATCGTCCAACGCAACGAATCCCTCTC 640 CCCCAACCAAATCGTCCAACCCAAAACCAATCCCTCTC 640 CCCAACCAAATCGGACGAACAAACCCTTCTC 640 CCCCAACCAAATCGGACGAACAAACCCTTCCAGCTCTC 640 CCCCAACCAAATCGGACGAACAAACCCTTCTCAACGCTTCTC 640 CCCCAACCAAATCGGACGAACAAACCCTTCTCAACGCTTCTC 640 CCCAACCAAATCGGACGAACAAACCCTTCTCAGCTCTCTATCACCCTTATCAACCCTTATCACCCTTATCAACCCTTATCACCCTTCTCAACCCAAATCCCTATCACCCTTTTTAAAAACGTCCTCATC

1. 1. 1. 1. 1. 1.

Fig. 11A (con't)

810	820	830	840		
AATTCTAGTGTGGACT					
TACTGAGAATGGCTGG				•	
CAAGATTCGTAACTCG					
TICATCITCTATCAAC					
CCCATTTCTTTCCTTC	CICAGCAACC	TCTCCACCACC	TTA 1000		
1010	1020	1030	1040		
<u> ئىسىلىسىلىسىلى</u>	بلينيليب	بيلينيان		· · · · · · · · · · · · · · · · · · ·	
TCAGCTGACATCGGCT	GAGIGCTACG	ATCTGAGGAGC	AAC 1040		
CGIGIGGITGCIGACCI				•	
ACATCAAACCCAAACC					
TCCTTGTCCAGCCAGT		•			•
TATGACCICIACCATO	CCTTCCTCG	JTGGGAGGCÇA	CC 1200	•	
1210	1220	1230	1240		
mulmulmul					
CATGGACCGCGTGCTCC					
GAGCCGGGCAGTTTCCT				•	
CATGICACTTCAGTGG			-		
CTAAGATGCCCATCGC					
CCCTAAATGGCTGGCAC	CAGGAGTGGT	CTCCGTGCACA	GTG 1400		
1410	1420	1430	1440	·	•
					
ACGIGIGGCCAGGGCCI					•
TCGACCATCGACGAATC					•
AACAAAGCCCCACATAA					
CCCTGCTATAAACCCAA					
AGTIGCCATGGTTCAA				,	
1610	1620	1630	1640		•
					
AGCTGCTGTGTCAGAGC	-				
cagactgttctatattt					
gtgtctcactggttgta			_		
tgtaatcatctcaccaa		="			•
gattgattagtttcaaa	1888888888	adaaaaga (gc	AAC TROO		•

Fig. 11A (con't)

	1810	1820	1830	1840		
لسب ا	ليتبليب	لتتبليينا	لسيلسن	ــــلىسـ	 	
agc 18	303		-			

Fig. 11B

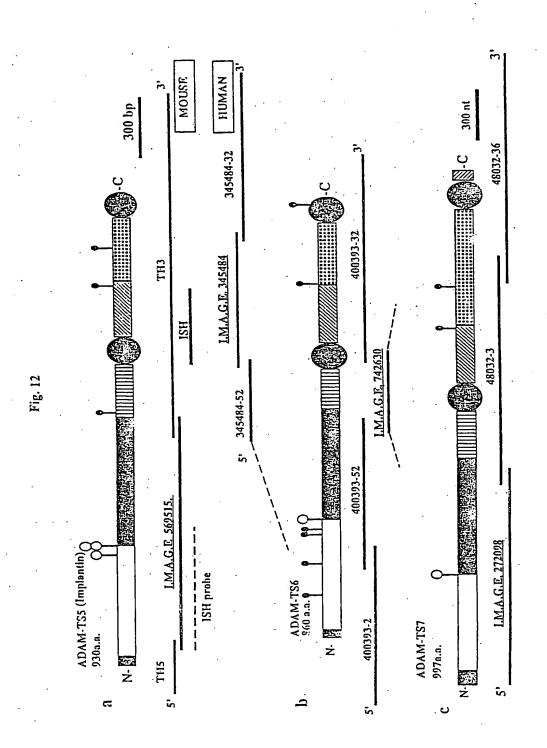
		•									
	Asp (D)	30	# cua	Leu(L)	3	# uca	Ser(S)	6	# guu	Val(V)	6
ugc	Cys (C)	26	# cuc	Leu(L)	11	# ucc	Ser(S)	10	#	Val(V)	29
ugu	Cys (C)	10	# cug	Leu(L)	14	# ucg	Ser(S)	5	# mm	???(X)	0
	Cys(C)	36	# cuu	Leu(L)	6	# ucu	Ser(S)	5	# TOTA	L	526
caa	Gln(Q)	7	# wua	Leu(L)	4	#	Ser(S)	43	#		

Created: Wednesday, May 5, 1999 10:19 AM

Ligated 459225+482392 with Sac I(168)&Eco RI(or Not I) Cloning site:5';Eco RI 3';Not I Vector; PT7T3 pac.

10 MECCRRATEGILLIFLAFLLLSSRTARSEEDROGLWDAWG 40 PWSECSRTCGGGAANSLRRCLSSKSCEGRNIRYRTCSNVD 80 CPPEAGDFRAQQCSAHNDVKHHGQFYEWLFVSNDFDNPCS 120 LKCQAKGITLVVELAPKVLDGTRCYTESLIMCISGLCQIV 160 GCDHQLGSTVKEDNCGVCNGDGSTCRLVRGQYKSQLSATK 200 210 220 230 Landard Landers Lander SDDTVVAIPYGSRHIRLVLKGPDHLYLETKTLQGTKGENS 240 LSSIGIFLVDNSSVDFQKFPDKETLRMAGPLTADFIVKIR 280 NSGSADSTVQFIFYQPIIHRWREIDFFPCSATCGGGYQLT 320 SAECYDLRSNRVVADQYCHYYPENIKPKPKLQECNLDPCP 360 ASDGYKQIMPYDLYHPLPRWEATFWIACSSSCGGGIQSRA 400 410 420 430 440 uluuluuluuluuluuluu VSCVEEDIQCHVTSVEEWKCMYTPKMPIAQPCNIFDCPKW 440 LAQEWSPCTVTCGQGLRYRVVLCTDHRGMHTGGCSFKTXP 480 HIKEBCIVPTPCYKPKEKLPVEAKLPWFKQAQELEEGAAV 520

SEEPS. 526



SUBSTITUTE SHEET (RULE 26)

u ·	
MRLEWASILLLLLLL SASCILSLANDSPAAAAAPAQDKTRQPQAAAAAAEPDQPCGEETRERGFLQPLAGQRRSGGLVHNITIC	. 20
LYSGOGKVGYLVYAGGRRFLLDLERDDIVGAAGSIVTAGGGLSASSGHRGHČFYRGIVDGSPRSLAVFDLČGGLDGFFAV	160
KHARYTI.KPILIPGSWAEYERIYGIGSSRIIHVYNREGFSFEALPPRASCETPASPSGPQESPSVHSRSRRRSALAPQILD	240
HSAFSPSZNAGPOTWIPPERRSISRARQVEILLVADESMARMYGRGIQHYLLTLASTANRLYSHASTENHTRLAWKWW	•
LIDKDISLEVSKVAATTLKVFČKOHOHOLGIDHEEHYDAATLFTREDLÖGHISÜDTLGVADVGITČSPERSÖAVIEDO	400
GLHAAFTVHEIGHLIGISHDSKECEENFGTTEDKRIMESTLTSTDASKFWSKCTSATTTEFLDOGKSVILJILPRKQI GHLIGISHDSKECEETFGSTEDKRIMESTLTSTDASKFWSKCTSATTTEFLDOGKSVILJILPRKQI Dis	. 4 80
LGPEELFGQTYDATQQCNLTFGFEYSVCFGMDVCARLWCAVVRQGMVCLTKKLPAVEGTFCGKGRVCLQGKCVDKTRKK LGPEELFGQTYDATQQCNLTFGFEYSVCFGXDVCARLWCAVVRQGMVCLTKKLPAVEGTFCGKGRLCLQGKCVDKTRKK	560
YYSTSSHQMGSWGWGQCSRSCCCGVQFAYRHOWPAPRNGGRYCTGKRALYRSCSVTRCPPNGKSFRHEQCEAKNGYQ YYSTSSHQM <u>MGSWCSWGQCSRSCCCGVQFAYRHOWPAPRNGRYCTGKRALYHSCSLMRC</u> PRNGKSFRHEQCEAKNGYQ	640
SDAKGVKTFVEWFKYAGVLPADVČKLIČRAKGIGYYVVFSPKVIDGTEČRPYSNSVČVRGRČVRIGČDGI IGSKLQYDK SDAKGVKTFVEWPKYAGVLPADVCKLICRAKGIGYYVVFSPKVIDGTECRPYSNSVCVRGKCVRIGCDGI IGSKLQYDK * *4— Spacer domain	
CGVCGGLNSSCTKLIGTFNKKSKGYTDWRLPEGATHLKVRQFKAKDQTRFPAYLALKKKTGEYLINGKYMLSTSETTID CGVCGGLNSSCTKLVGTFNKKSKGYTDWRLPEGATHLKVRQFKAKDQTRFTAYLALKKKNGEYLINGKYMLSTSETTID	
INGIVANYSCWSHRODFI HOMGYSATKETLIVQILATOPIKALGVRYSFFVPKKTIQKVNSVISHGSNKVGPHSTQLQWV INGIVANYSGWSHRODFI HOMGYSATKETLIVQILATOPIKPLOVRYSFFVPKKSTFKVNSVISHGSNKVGSHISQFQWV	880
IGFWLACSRICDIGWHIRIVOCODONRKLAKGCILSORPSAFKOCILKKC IGFWLACSRICDIGWHIRIVOCODONRKLAKGCIPLSORPSAFKOCILKKC	930

Fig. 13

MEILWKILIWILSLIMASSEFHSLIKELSYSSQEETLIYLEHYQLITIPIRVOQGAFLSFTVMIKKISRRRRYDPIDFQQ 80

AVSKLIFIKLSAYGKIFHINLITUNDFVSKIFTVEYWKKDERWKHDFLINCYYTGYLQDRSTTKVALSKVEHGVIAT 160

EDETYFIEPLKNITELSKIFSYENGHENVIYKKSALQORHLYLHSHCGVEFTRSGKEWMINDISTVSYSLFINNIHIH 240

RQKFSVSIERFVETLWALKMAVGYHERKDIENYILSVANIVAKLYRDSSLQWWNILVARLIVLTEDQRALFINNHALK 320

SLDSFCKWKSILSHQSDNITPENGIAHINAVLITRYDICTYKKFGGTILG ASVANTEPERSCSINEDIGLGSAFT 400

LIFETVANFQAHDGIQASCERKIRQONYGSSHYCEYQSFFLWLQSRLHHQLFREVCREIWCLSKANCVINSTPAAE 480

GILQQUONEKGAYQGDVFFGIWPQSIIDSGHWSLWGECSRICGGGSSSSLRHCDSPASSGGKYLGERKRYFSÖN 560

TDPCPLGSRDFREKQÖADFINNFFRGKYMWRYTGGSVKPÖALNÜABGANFYTERAPAVIDGTQAADSIDICTNEE 640

TDPCPLGSRDFREKQÖADFINNFFRGKYMWRYTGGSVKPÖALNÜABGANFYTERAPAVIDGTQAADSIDICTNEE 640

MANGINILGSDAREIRCRVGGGSSTCHAIGFFRDSLFRGGMEWVQIPRGSVHIEVREVAMSKNYIALKSEGDDYYI 720

MANTIDWFRKEDVAGTAFHYKRPIDEPESLFALGPTSENLIVMVLQBONLGIRYKFNVPITRIGSGINEVEFTWHQP 800

CC

MEGGPSPRSPAFLIRPILLILLCALAFGARGPARGFATEERAALDIVHPVRVDAGGSFLSYELWFRALRKRUVSVRRDAPA 80

FYYELQYRGPELRFNLTANGHILAFGFVSETFRRGSLGRAHIFAHTPACHLIGEVQDFEIBGGAAISAÖCGLKGVFQLSN 160

EDYF IEPIDSAPARRHAQPHVVYKRQAPERLAQKGDSSAPSTCGVVYFELESRREWEGROAWRRPRIRRIHGRSVSK 240

EKWETLWADAKMVEYHQQPQVESYVLITDAMVAGLFHDPSIGQPIHTITVRIVILLEDEEDLKITHHAINTIKSFCTW 320

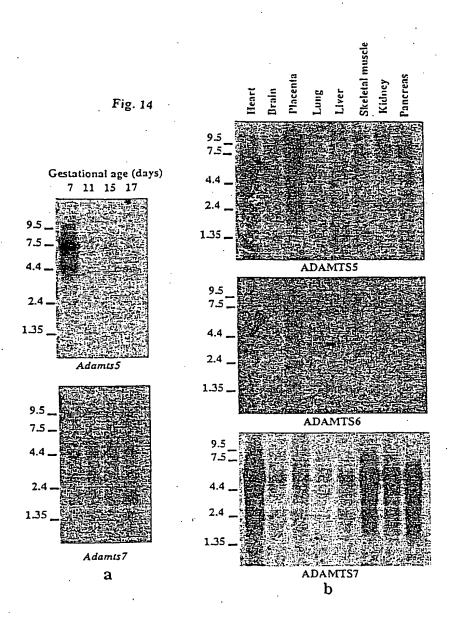
OKSINMKGDAHPEHHUTA II LITEKDI CAAMNREETILGLSHVARCDPHRSTSINFITGE ELAFTVARFI CHSESIGHTG 400

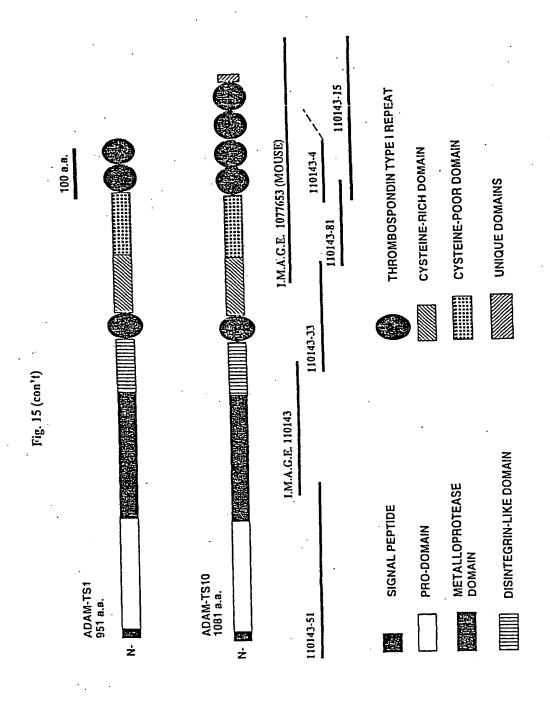
Fig. 13 (con't)

. CWATTGLEVCFSEPOFSICEMRLAIALCPPPAGRVHG 997

		adamalysin II atrolysin A	HELGHNLGME HD HELGHNLGMV HD	
	a	hADAM-9 hADAM-10 hADAM-15 hADAM-17 mADAM-19	HELGHNÌGMNHD HEVGHNFGSPHD HELGHSLGLDHD HELGHNFGAEHD HEIGHNFGMSHD	
	a	mADAM-TS1 hADAM-TS2 hADAM-TS3 hADAM-TS4 mADAM-TS5 hADAM-TS6 hADAM-TS7	HELGHVFNMP HD HETGHVLGME HD HETGHVLGME HD HELGHVFNML HD HEIGHL LG LS HD HEIVHN FGMNHD HELGH S FG I Q HD	
	mADAM-TS1 hADAM-TS2 hADAM-TS3 hADAM-TS4 hADAM-TS5 hADAM-TS6 hADAM-TS7	W G P W G P W G A W S P W G P W G S W G S W G P W S L W S G W S A	W G D C S R T C G G G V Q Y F G S C S R T C G T G V K F F G S C S R T C G G G V Q F W G D C S R T C G G G V Q F W G E C S R T C G G G V S S W G E C S R T C G G G V S S W G E C S R T C G G G V S S	20 20 20 20 20 20 20 20
b	mADAM-TSI hADAM-TS2 hADAM-TS3 hADAM-TS4 hADAM-TS5 hADAM-TS6 hADAM-TS7	T M R E C D R T R Q C D R T R Q C D S S R D C T A Y R H C D A E R Q C T		40 40 40 40 40 40
	mADAM-TSI hADAM-TS2 hADAM-TS3 hADAM-TS4 hADAM-TS5 hADAM-TS6 hADAM-TS7	R V R Y R S A Y D F Q L A Y D F Q L R T R F R S R A I Y H S R K R Y R S R K R F R L	C N F D C C N S Q D C C N T E D C C N T E D C C N T E D C C N T D P C C N T D P C	52 52 52 52 52 52 52 52 52

Fig. 13 (con't)





SUBSTITUTE SHEET (RULE 26)

UNIQUE DOMAINS

DISINTEGRIN-LIKE DOMAIN

ADAM-TS RELATED PROTEIN-1 (ADAM-TSR1) 100 а.а. ADAM-TS1 951 a.a.

Fig. 15

THROMBOSPONDIŅ TYPE I REPEAT CYSTEINE-POOR DOMAIN CYSTEINE-RICH DOMAIN ADAM-TSR1 525 a.a. METALLOPROTEASE DOMAIN SIGNAL PEPTIDE PRO-DOMAIN

SUBSTITUTE SHEET (RULE 26)

FIGURE 16

MSSCPVWPAMRSPSPPAWTTTGHCWPSRHLLP 40 GAAPRHGGHSRVPPLLQSGLASTHFLLNLTRSSRLLAGRV 80 SVEYWIREGLAWQRAARPHCLYAGHLQGQASSSHVAISTC 120 GGLHGLIVADEEEYLIEPLHGGPKGSRSPEESGPHVVYKR 160 SSLRHPHLDTACGVRDEKPWKGRPWWLRTLKPPPARPLON 200 ETERGOPGLKRSVSRERYVETLVVADKMMVAYHGRRDVEQ 240 YVLAIMNIVAKLFQDSSLGSIVNILVIRLILLIEDQPILE 280 ITHHAGKSLDSFCKWQKSIVNHSGHGNAIPENGVANHDTA 320 VLITRYDICTYKNKPOGILGLARWAECVSAREAAASMRIL 360 AATSVHHCHEIGHIFGMVHDGVGNSCGARGQDPAKLMAAH 400 ITMKINPFVWSSCNRDYITSFLDSGLGLCLNNRPPRQDFV 440 YPTVAPGQAYDADEQCRFQHGVKSRQCKYGEVCSELWCLS 480 KSNRCIINSIPAAEGILQQIHTIDKGWCYKRVCVPFGSRP 520 EGVDGAWGPWTPWGDCSRTCGGGVSSSSRHCDSPRPTTGG 560 KYCLGERRRHRSCNIDDCPPGSQDFREVQCSEFDSIPFRG 600 KFYKWKTYRGGGVKACSLTSLAEGFNFYTERAAAVVDGTP 640 CRPDIVDICVSGECKHVGCDRVLGSDLREDKCRVCGGDGS 680 ACETIEGVFSPASPGAGYEDVVWIPKGSVHIFIQDLNLSL 720 SHLALKGDQESLLLEGLPGTPQPHRLPLAGTTFQLRQGPD 760 QVQSLEALGPINASLIVMVLARTELPALRYRFNAPIARDS 800 LPPYSWHYAPWIKCSAQCAGGSQVQAVECRNQLDSSAVAP 840 HYCSAHSKLPKRORACNTEPCPPDWVVGWSLCSRSCDAG 880 VRSRSVVCQRRVSAAEEKALDDSACPQPRPPVLEACHGPT 920 CPPEWAALDWSECTPSCGPGLRHRVVLCKSADHRATLPPA 960 HCSPAAKPPATMRCNLRRCPPARWAGEWGECSAQCGVGO 1000 RQRSVRCTSHTGQASHECTEALRPPTTQQCEAKCDSPTPG 1040 DGPEECKDVNKVAYCPLVLKFQFCSRAYFRQMCCKTCQGH 1080 Created: Thursday, October 01, 1998 11:05 PM

	10	20	30	40	
سلست	ستثلث	سيبلينين	سيلسين	لبيبيا	
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TCTGGAC	SAGCTATG	AGATCGCCTT	CCCCACCCG	CGTGGAC	80
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and market and an arrange of the second seco
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لسيلسيلسي	لتتسليب	سيلسب	<u> </u>		
ggggatgga 3409					

FIGURE 17

Molecular Weight 216301.30 Daltons 1934 Amino Acids 234 Strongly Basic(+) Amino Acids (K,R) 216 Strongly Acidic(-) Amino Acids (D,E) 477 Hydrophobic Amino Acids (A,I,L,F,W,V) 657 Polar Amino Acids (N,C,Q,S,T,Y)

7.734 Isolectric Point 24.102 Charge at PH 7.0

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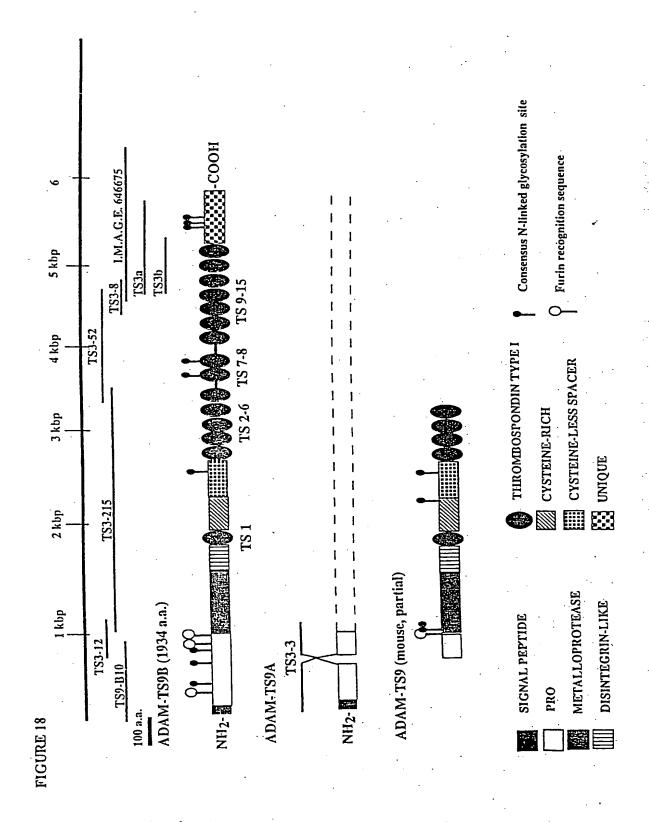
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135

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45	Leu	Ser 290	Tyr	Pro	Arg	Phe	Val 295	Glu	Val	Leu	Val	Val 300	Ala	Asp	Asn	Arg
50	Met 305	Val	Ser	Tyr	His	Gly 310	Glu	Asn	Leu	Gln	His 315	Tyr	Ile	Leu	Thr	Leu 320
30	Met	Ser	Ile	Val	Ala 325	Ser	Ile	Tyr	Lys	Asp 330	Pro	Ser	Ile	Gly	Asn 335	Leu
55	Ile	Asn	Ile	Val 340	Ile	Val	Asn	Leu	11e 345	Val	Ile	His	Asn	Glu 350	Gln	Asp
	Gly	Pro	Ser 355	Ile	Ser	Phe	Asn	Ala 360	Gln	Thr	Thr	Leu	Lys 365	Asn	Phe	Cys
60	Gln	Trp 370	Gln	His	Ser	Asn	Ser 375	Pro	Gly	Gly	Ile	His 380	His	Asp	Thr	Äla
65	Val 385	Leu	Leu	Thr	Arg	Gln 390	Asp	Ile	Cys	Arg	Ala 395	His	Asp	Lys	Cys	Asp 400
93	Thr	Leu	Gly	Leu	Ala	Glu	Leu	Gly	Thr	Ile	Cys	Asp	Pro	Tyr	Arg	Ser

					405					410					415	
5	Cys	Ser	Ile	Ser 420	Glu	Asp	Ser	Gly	Leu 425	Ser	Thr	Ala	Phe	Thr 430	Ile	Ala
J	His	Glu	Leu 435	Gly	His	Val	Phe	Asn 440	Met	Pro	His	Asp	Asp 445	Asn	Asn	Lys
10	Cys	Lys 450	Glu	Glu	Gly	Val	Lys 455	Ser	Pro	Gln	His	Val 460	Met	Ala	Pro	Thr
	Leu 465	Asn	Phe	Tyr	Thr	Asn 470	Pro	Trp	Met	Trp	Ser 475	Lys	Cys	Ser	Arg	Lys 480
15	Tyr	Ile	Thr	Glu	Phe 485	Leu	Asp	Thr	Gly	Tyr 490	Gly	Glu	Cys	Leu	Leu 495	Asn
20	Glu	Pro	Glu	Ser 500	Arg	Pro	Tyr	Pro	Leu 505	Pro	Val	Gln	Leu	Pro 510	Gly	Ile
20	Leu	Tyr	Asn 515	Val	Asn	Lys	Gln	Cys 520	Glu	Leu	Ile	Phe	Gly 525	Pro	Gly _/	Ser
25	Gln	Val 530	Cys	Pro	Tyr	Met	Met 535	Gln	Cys	Arg	Arg	Leu 540	Trp	Ser	Asn	Asn
	Val 545	Asn	Gly	Val	His	Lys 550	Gly	Сув	Arg	Thr	Gln 555	His	Thr	Pro	Trp	Ala 560
30	Asp	Gly	Thr	Glu	Сув 565	Glu	Pro	Gly	Lys	His 570	Сув	Lys	Туr	Gly	Phe 575	Cys
35	Val	Pro	Lys	Glu 580	Met	Asp	Val	Pro	Val 585	Thr	Asp	Gly	Ser	Trp 590	Gly	Ser
,,,	Trp	Ser	Pro 595	Phe	Gly	Thr	Cys ·	Ser 600	Arg	Thr	Cys	Gly	Gly 605	Gly	Ile	Lys
40	Thr	Ala 610	Ile	Arg	Glu	Cys	Asn 615	Arg	Pro	Glu	Pro	Lys 620	Asn	Gly	Gly	Lys
	Tyr 625	Cys	Val	Gly	Arg	Arg 630	Met	Lys	Phe	Lys	Ser 635	Cys	Asn	Thr	Glu	Pro 640
45	Cys	Leu	Lys	Gln	Lys 645	Arg	Asp	Phe	Arg	Asp 650	Glu	Gln	Сув	Ala	His 655	Phe
50	Asp	Gly	Lys	His 660	Phe	Asn	Ile	Asn	Gly 665	Leu	Leu	Pro	Asn	Val 670	Arg	Trp
	Val	Pro	Lys 675	туг	Ser	Gly	Ile	Leu 680	Met	Lys	Asp	Arg	Cys 685	Lys	Leu	Phe
55	Cys	Arg 690	Val	Ala	Gly	Asn	Thr 695	Ala	Tyr	Tyr	Gln	Leu 700	Arg	Asp	Arg	Val
	Ile 705	Asp	Gly	Thr	Pro	Сув 710	Gly	Gln	Asp	Thr	Asn 715	Asp	Ile	Суз	Val	Gln 720
60	Gly	Leu	Cys	Arg	Gln 725	Ala	Gly	Сув	Asp	His 730	Val	Leu	Asn	Ser	Lys 735	Ala
65	Arg	Arg	Asp	Lys 740	Cys	Gly	Val	Cys	Gly 745	Gly	Asp	Asn	Ser	Ser 750	Сув	Lys
0.5	Thr	Val	Ala	Gly	Thr	Phe	Asn	Thr	Val	His	Tyr	Gly	Tyr	Asn	Thr	Val

755 760 765 Val Arg Ile Pro Ala Gly Ala Thr Asn Ile Asp Val Arg Gln His Ser 775 Phe Ser Gly Glu Thr Asp Asp Asp Asn Tyr Leu Ala Leu Ser Ser Ser Lys Gly Glu Phe Leu Leu Asn Gly Asn Phe Val Val Thr Met Ala Lys 810 Arg Glu Ile Arg Ile Gly Asn Ala Val Val Glu Tyr Ser Gly Ser Glu 825 15 Thr Ala Val Glu Arg Ile Asn Ser Thr Asp Arg Ile Glu Gln Glu Leu Leu Leu Gln Val Leu Ser Val Gly Lys Leu Tyr Asn Pro Asp Val Arg 20 Tyr Ser Phe Asn Ile Pro Ile Glu Asp Lys Pro Gln Gln Phe Tyr Trp Asn Ser His Gly Pro Trp Gln Ala Cys Ser Lys Pro Cys Gln Gly Glu 890 Arg Lys Arg Lys Leu Val Cys Thr Arg Glu Ser Asp Gln Leu Thr Val 905 30 Ser Asp Gln Arg Cys Asp Arg Leu Pro Gln Pro Gly His Ile Thr Glu 920 Pro Cys Gly Thr Gly Cys Asp Leu Arg Trp His Val Ala Ser Arg Ser 935 35 Glu Cys Ser Ala Gln Cys Gly Leu Gly Tyr Arg Thr Leu Asp Ile Tyr Cys Ala Lys Tyr Ser Arg Leu Asp Gly Lys Thr Glu Lys Val Asp Asp Gly Phe Cys Ser Ser His Pro Lys Pro Ser Asn Arg Glu Lys Cys Ser 980 985 45 Gly Glu Cys Asn Thr Gly Gly Trp Arg Tyr Ser Ala Trp Thr Glu Cys 1000 Ser Lys Ser Cys Asp Gly Gly Thr Gln Arg Arg Ala Ile Cys Val 1015 Asn Thr Arg Asn Asp Val Leu Asp Asp Ser Lys Cys Thr His Gln Glu 1030 1035 Lys Val Thr Ile Gln Arg Cys Ser Glu Phe Pro Cys Pro Gln Trp Lys 1050 Ser Gly Asp Trp Ser Glu Cys Leu Val Thr Cys Gly Lys Gly His Lys 1065 60 His Arg Gln Val Trp Cys Gln Phe Gly Glu Asp Arg Leu Asn Asp Arg 1080 Met Cys Asp Pro Glu Thr Lys Pro Thr Ser Met Gln Thr Cys Gln Gln 1095 Pro Glu Met Ala Ser Trp Gln Ala Gly Pro Trp Val Gln Cys Ser Val

	1105		111	ס		1115		1120
5	Thr Cys		Gly Ty: 1125	r Gln Le	u Arg Ala 1130		Cys Ile	lle Gly
•	Thr Tyr	Met Ser 1140	Val Va	l Asp As	p Asn Asp 1145	Cys Asn	Ala Ala 1150	
10		Asp Thr 1155	Gln Ası	Cys Gl: 116	u Leu Pro O		His Pro 1165) Pro Pro
	1170			1175	r Thr Tyr	1180		
15	Trp Arg 1185	Phe Gly	Ser Tr		o Cys Ser	Ala Thr 1195	Cys Gly	Lys Gly
20	Thr Arg		Tyr Val 1205	. Ser Cyı	s Arg Asp 1210	Glu Asn	Gly Ser	Val Ala 1215
	Asp Glu	Ser Ala 1220	Cys Ala	Thr Le	Pro Arg 1225	Pro Val	Ala Lys 1230	
25		Val Thr 1235	Pro Cys	1240	n Trp Lys)		Asp Trp 1245	Ser Ser
	Cys Ser 1250	Val Thr	Cys Gly	Gln Gly	y Arg Ala	Thr Arg 1260	Gln Val	Met Cys
30	Val Asn 1265	Tyr Ser	Asp His		e Asp Arg	Ser Glu 1275	Cys Asp	Gln Asp 1280
35	Tyr Ile		Thr Asp 1285	Gln Ası	Cys Ser 1290	Met Ser	_	Pro Gln 1295
	Arg Thr	Pro Asp 1300	Ser Gly	Leu Ala	Gln His 1305	Pro Phe	Gln Asn 1310	
10		Pro Arg 1315	Ser Ala	Ser Pro	Ser Arg		Val Leu 1325	Gly Gly
	Asn Gln 1330	Trp Arg	Thr Gly	Pro Trp 1335	Gly Ala	Cys Ser 1340	Ser Thr	Cys Ala
15	Gly Gly 1345	Ser Gln	Arg Arg		. Val Cys	Gln Asp 1355	Glu Asn	Gly Tyr 1360
50	Thr Ala		Cys Val 1365	Glu Arg	Ile Lys 1370	Pro Asp		Arg Ala 1375
	Cys Glu	Ser Gly 1380	Pro Cys	Pro Glr	Trp Ala 1385	Tyr Gly	Asn Trp 1390	
55	Cys Thr	Lys Leu .395	Cys Gly	Gly Gly 1400	Ile Arg		Leu Val 1405	Val Cys
	Gln Arg 1410	Ser Asn	Gly Glu	Arg Phe	Pro Asp	Leu Ser 1420	Cys Glu	Ile Leu
50	Asp Lys 1425	Pro Pro	Asp Arg 1430	Glu Glr	Cys Asn	Thr His	Ala Cys	Pro His 1440
55		· 1	1445		Trp Ser 1450		;	1455
	Gly Arg	Gly His	Lys Gln	Arg Asn	Val Tyr	Cys Met	Ala Lys	Asp Gly

1460 1465 1470

Ser His Leu Glu Ser Asp Tyr Cys Lys His Leu Ala Lys Pro His Gly 1475 1480 1485

His Arg Lys Cys Arg Gly Gly Arg Cys Pro Lys Trp Lys Ala Gly Ala 1490 1495 1500

Trp Ser Gln Cys Ser Val Ser Cys Gly Arg Gly Val Gln Gln Arg His 10 1505 1510 1515 1520

Val Gly Cys Gln Ile Gly Thr His Lys Ile Ala Arg Asp Thr Glu Cys 1525 1530 1535

15 Asn Pro Tyr Thr Arg Pro Glu Ser Glu Cys Glu Cys Gln Gly Pro Arg 1540 1545 1550

Cys Pro Leu Tyr Thr Trp Arg Ala Glu Glu Ser Gln Glu Cys Thr Lys 1555 1560 1565

Thr Cys Gly Glu Gly Ser Arg Tyr Arg Lys Val Val Cys Val Asp Asp 1570 1575 1580

Asn Lys Asn Glu Val His Gly Ala Arg Cys Asp Val Ser Lys Arg Pro 25 1585 1590 1595 1600

Val Asp Arg Glu Ser Cys Ser Leu Gln Pro Cys Glu Tyr Val Trp Ile 1605 1610 1615

30 Thr Gly Glu Trp Ser Glu Cys Ser Val Thr Cys Gly Lys Gly Tyr Lys 1620 1625 1630

Gln Arg Leu Val Ser Cys Ser Glu Ile Tyr Thr Gly Lys Glu Asn Tyr 1635 1640 1645

Glu Tyr Ser Tyr Gln Thr Thr Ile Asn Cys Pro Gly Thr Gln Pro Pro 1650 1655 1660

Ser Val His Pro Cys Tyr Leu Arg Glu Cys Pro Val Ser Ala Thr Trp 40 1665 1670 1675 1680

Arg Val Gly Asn Trp Gly Ser Cys Ser Val Ser Cys Gly Val Gly Val 1685 1690 1695

45 Met Gln Arg Ser Val Gln Cys Leu Thr Asn Glu Asp Gln Pro Ser His 1700 1705 1710

Leu Cys His Thr Asp Leu Lys Pro Glu Glu Arg Lys Thr Cys Arg Asn 1715 1720 1725

Val Tyr Asn Cys Glu Leu Pro Gln Asn Cys Lys Glu Val Lys Arg Leu 1730 1735 1740

Lys Gly Ala Ser Glu Asp Gly Glu Tyr Phe Leu Met Ile Arg Gly Lys 55 1745 1750 1755 1760

Leu Leu Lys Ile Phe Cys Ala Gly Met His Ser Asp His Pro Lys Glu 1765 1770 1775

60 Tyr Val Thr Leu Val His Gly Asp Ser Glu Asn Phe Ser Glu Val Tyr 1780 1785 1790

Gly His Arg Leu His Asn Pro Thr Glu Cys Pro Tyr Asn Gly Ser Arg 1795 1800 1805

Arg Asp Asp Cys Gln Cys Arg Lys Asp Tyr Thr Ala Ala Gly Phe Ser

1810 1815 1820

Ser Phe Gln Lys Ile Arg Ile Asp Leu Thr Ser Met Gln Ile Ile Thr 1825 1830 1835 1840

Thr Asp Leu Gln Phe Ala Arg Thr Ser Glu Gly His Pro Val Pro Phe 1845 1850 1855

Ala Thr Ala Gly Asp Cys Tyr Ser Ala Ala Lys Cys Pro Gln Gly Arg 10 1860 1865 1870

Phe Ser Ile Asn Leu Tyr Gly Thr Gly Leu Ser Leu Thr Glu Ser Ala 1875 1880 1885

15 Arg Trp Ile Ser Gln Gly Asn Tyr Ala Val Ser Asp Ile Lys Lys Ser 1890 1895 1900

Pro Asp Gly Thr Arg Val Val Gly Lys Cys Gly Gly Tyr Cys Gly Lys 1905 1910 1915 1920

Cys Thr Pro Ser Ser Gly Thr Gly Leu Glu Val Arg Val Leu 1925 1930

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